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TOPIC HIGHLIGHT

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Colonic polyps: Is it useful to characterize them with advanced endoscopy?

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Abstract

There have been major developments in endoscopic imaging techniques in recent years. Endoscopes with high definition and magnification can provide high quality images that allow for the histological estimation of lesions *in vivo* and *in situ* when combined with ancillary enhancement techniques such as chromoendoscopy (CE) and virtual CE (narrow band imaging fujinon intelligent chromoendoscopy, or i-Scan). Despite the enormous potential for these advanced techniques, their value and feasibility in the clinic are still doubted, particularly in cases of colonic polyps that are slated for removal, where *in vivo* characterization may be deemed unnecessary. However, there are several advantages offered by such advanced endoscopic imaging. CE with or without magnification demonstrates highly accurate histology and invasion depth prediction, and virtual CE is a feasible and less cumbersome alternative to CE in terms of histological estimation, though not sufficiently accurate for depth invasion prediction. Furthermore, the supplementary information provided by advanced imaging systems can assist the endoscopist in the selection of a strategic approach, such as in deciding whether a colonic lesion should be resected, left *in situ*, or requires more intensive surgical treatment. Lastly, advanced high-resolution imaging techniques may be more cost effective, such that histopathology of low-risk lesions following resection can be eliminated. The results of these evaluations and comparisons with traditional CE are presented and discussed. Taken together, the benefits provided by these advanced capabilities justify their development, and advocates their use for the treatment and management of colonic polyps.

Key words: Colon polyps; Chromoendoscopy; Narrow band imaging; Fujinon intelligent chromoendoscopy; i-Scan; Colonoscopy; Optical biopsy

Core tip: Endoscopic characterization of colonic polyps by "virtual histology" is a currently accessible tool for identification of lesion type, thus enabling endoscopists to determine optimal treatment strategies. Chromoendoscopy (CE) has shown high accuracy for differentiating polyp histologies (neoplastic *vs* non-neoplastic) and for estimating the depth of invasion. Furthermore, digital systems such as narrow band imaging are a viable alternative to CE regarding lesion characterization, ease of use, reversibility, and cleanliness.

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COLORECTAL CANCER

Colorectal cancer (CRC) is the second most common cancer in women and the third most common in men from developed countries[1], which contrasts with the preventable nature of gastrointestinal cancers. While colorectal adenomas have long been considered as CRC precursors, recent evidence shows that that 20%-30% of all CRCs emerge from a distinct group of lesions, generically named serrated polyps, consisting of traditional serrated adenomas, sessile serrated adenomas (SSA) and hyperplastic polyps (HP)[2]. While HPs are generally understood to show little or no potential for degeneration, the other serrated polyps are capable of malignant transformation, similar to classic adenomas[3]. Currently, endoscopy is the most viable method for CRC prevention, which not only allows for diagnosis, but also for the removal of premalignant lesions. Furthermore, in addition to its preventative effects, endoscopic polypectomy has also been shown to reduce CRC mortality[4].

VIRTUAL HISTOLOGY

Substantial progress in the advancement of endoscopic imaging has been achieved in recent years. The acquisition of higher quality images allows for visualization of subtle details in the gastrointestinal mucosa. Prediction of lesion type prior to histological processing is made possible through examination of mucosal surface architecture and microvasculature, a method referred to as "virtual histology" or "optical biopsy."

The prediction of polyp histology and degree of invasion depth that can be ascertained with virtual histology has important therapeutic implications. Before resecting a lesion, the endoscopist must determine if the lesion contains an invasive cancer, if it can be left *in situ*, and if required, what the optimal resection method is. Enhanced endoscopic imaging can assist the endoscopist in these determinations. Whereas resection of small HPs ($\leqslant$ 5 mm) of the rectum and sigmoid colon, juvenile polyps and inflammatory polyps is not necessary considering their non-existent potential for degeneration, endoscopic resection is generally suitable for the remaining lesion types, excluding those containing cancer foci in deeper layers that require surgical management. Tumors with superficial submucosal invasion ($<$ 1000 μm, Vienna classification sm-1)[5] have a negligible rate of lymph node metastasis. Hence, endoscopic resection of these lesions may be the definitive treatment provided they are well- or moderately-differentiated, do not show vascular or lymphatic invasion, and the resection margin is $>$ 1 mm[6]. Importantly, these types of lesions can be accurately identified as a result of advancements in endoscopic imaging and ancillary techniques.

High-definition endoscopes display images of a superior quality, and the use of magnification devices allows for a highly detailed inspection of the mucosal surface. Whereas amplified digital images lack sharpness, these optical systems can achieve a × 150 magnification without loss of resolution[7]. In addition to these advances, there are auxiliary enhancement techniques that provide additional detail. The use of optical systems is generally implied in studies using magnification, yet endoscopes providing optical magnification are not available in the United States or in Europe (with some exceptions in the United Kingdom and a few other European centers). Thus, studies using this technology are mainly from Asian countries.

CHROMOENDOSCOPY

Chromoendoscopy (CE) is the topical instillation of dye through an endoscope channel to highlight small details of the mucosa. The two most commonly used dye types are vital or absorptive dyes that are taken up by intestinal cells, such as methylene blue and crystal violet, and contrast dyes such as indigo carmine, which are deposited in the mucosal grooves and enhance subtle mucosal unevenness. Before the dyes are administered, a solution containing mucolytic and de-foaming agents (for example, 300 mg of N-acetylcysteine and 100 mg of simethicone per liter of water) is pumped through the tissue to remove mucus and fecal remains. Dyes can be applied with a catheter for the staining of large mucosal areas (Figure 1), or directly through the endoscope channel with the aid of a syringe (Figure 2) (*e.g.*, 5 cc of dye followed by 15 cc of air in a 20 cc syringe) for occasional application. Absorptive contrasts should be left to stand after instillation for one minute before rinsing. Generally, methylene blue is used at a concentration of 0.1%, while indigo carmine is used at concentrations of 0.1%-0.5% for large and small areas, respectively. Due to its potential toxicity[7], 0.05% crystal violet should be applied in small quantities with a special non-traumatic catheter combined with magnification devices.

CE has been reliably used to distinguish neoplastic from non-neoplastic lesions. Additionally, it can predict the degree of invasion of colorectal tumors with high accuracy. Pit patterns of colonic lesions have been classified by Kudo *et al*[8] into seven categories (Table 1). To simply this complex classification for clinical use, pit patterns are grouped into three basic types: non-neoplastic lesions, Kudo I or II that do not require treatment (Figure 3A); Kudo non-invasive neoplasia, Kudo IIIs, IIIL, IV and selected cases of Vi, corresponding to adenomas and cancers with superficial submucosal invasion that are endoscopically treatable (Figure 3B); and invasive, Kudo V n and some Vi, requiring surgical treatment due to deep submucosal invasion[9]. Invasive patterns are typically not evenly distributed throughout the lesion, and usually found in lesions located in confined areas with steep edges, depressions or nodules larger than 1 cm, thereby necessitating the use of magnification for identification. Using magnification endoscopy for pit pattern assessment, Japanese studies have demonstrated that neoplastic lesions can be distinguished from non-neoplastic lesions with an accuracy of up to 99.1%[10], and the degree of invasion (superficial *vs* deep) can be estimated in up to

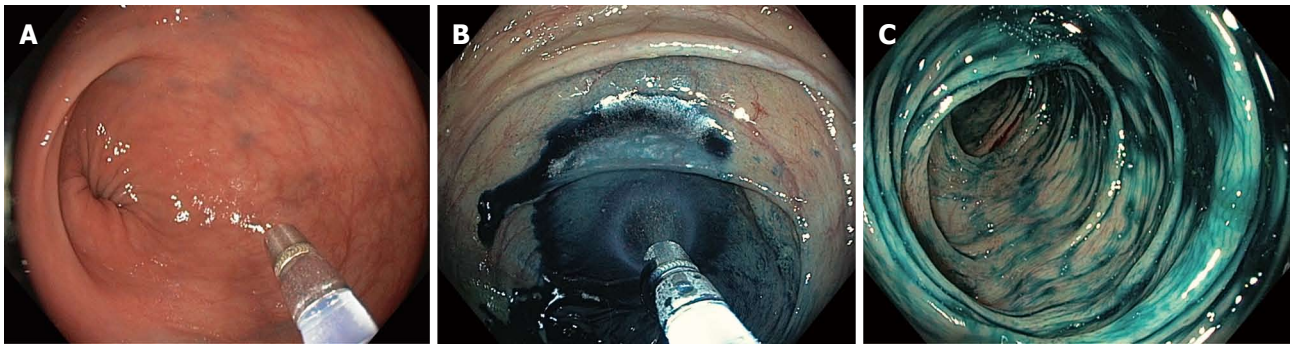

Figure 1 Indigo carmine staining for chromoendoscopy. A: Colorectal mucosa after cleansing with mucolytic and de-foaming agents; B: Instillation of dye using a spray catheter; C: Indigo carmine staining result.

Figure 2 Local application of chromoendoscopy with a single-use syringe through the endoscope channel.

98.8% of cases[11]. Furthermore, the application of these pattern assessments shows inter- and intra-observer agreement of 72%-86%[12]. CE using high-resolution endoscopes without magnification also allows for differentiation of neoplastic from non-neoplastic lesions, though with slightly reduced accuracy (87%-92%)[13-16].

The recent rise in cases of serrated polyps (SP) highlights limitations in the simple categorization of neoplastic and non-neoplastic lesions for identification of malignant types. Although SPs are generally non-neoplastic and show no dysplasia, their resection is indicated considering their potential for malignancy[17], except in instances of diminutive ($\leqslant$ 5 mm) HPs in the rectum or sigmoid colon. These HPs are not considered malignant and so can be left *in situ*. Consequently, the method for classification should be amended to accurately distinguish between adenoma, SSA and HP lesion types. Specifically, endoscopic differentiation between SSA and HP is indeed valuable as not all serrated lesions have the same malignant potential, with some indications that HPs can have a more benign behavior than SSAs and adenomas, though both HPs and diminutive SSAs can be located in the sigmoid colon and rectum. Although medical literature regarding endoscopic characterization of SPs is heterogeneous and often confusing, SSAs and HPs are typically described as pale and flat lesions, exhibiting poorly defined edges and often a layer of mucus or stool attached to their surface. The pit pattern in SSA was evaluated in a Japanese study with CE and magnification. A new category with wider and rounder crypts was thus described (type Ⅱ-O) (Figure 4), which results in a more accurate (81%) diagnosis of SSA[18].

DIGITAL CE

For its proven clinical applications, CE represents the benchmark for enhanced imaging techniques that have been subsequently developed. However, as the technique is labor- and time-intensive, CE has not been universally implemented, and thus has precipitated the development of several digital CE devices. Digital CE techniques provide similar information to standard CE, with the advantage of reversibility (turned on and off by pressing a button on the head of the endoscope), speed, and hygiene. All of them provide a high-resolution image. The first system marketed was narrow band imaging (NBI) by Olympus Medical Systems (Tokyo, Japan). Latter systems were designed and commercialized to provide a similar view *via* digital image post-processing, such as fujinon intelligent chromo endoscopy (FICE) from Fujinon (Saitama, Japan) and i-Scan from Pentax (Tokyo, Japan).

NBI is an endoscopic enhancement tool based on spectrum filtration to only allow the passage of green and blue light, thereby providing contrasted images that highlight subtle mucosal changes, revealing the inner structure and vascular pattern of the tissue. Thus, NBI provides information not only on the surface architecture as traditional CE, but also on vascularization, both of which are altered in neoplastic lesions of the gastrointestinal tract. Comparisons of Kudo's pit patterns determined by NBI and CE show considerable but not total agreement[19-21]. NBI allows for the evaluation of vascularization intensities with relative ease, which are often not consistently reported, providing diagnostic accuracy equal or superior to the pit pattern[22,23]. Neoplastic lesions exhibit a dark color due to high vascularity, in contrast with lighter-colored non-neoplastic tissues. The combination of pit pattern and vascularization intensity is the most common diagnostic criterion, reaching a high diagnostic accuracy with (90%-91%)[22,23] and without (80%-95%)[24-28] magnification (Figure 5).

Several classification strategies have been documented

Table 1 Pit pattern classification

Kudo *et al*[8] class	Description	Most likely histology	Neoplastic/non-neoplastic	Treatment
I	Round crypts	Normal mucosa	Non-neoplastic	None
II	Regular wider or stellar crypts	Hyperplastic polyp (also sessile serrated adenomas)	Non-neoplastic	None if rectosigmoid and ≤ 5 mm/ endoscopic resection
IIIL	Elongated or roundish crypts	Adenoma	Neoplastic	Endoscopic resection
IIIs	Tubular or roundish pits smaller than the normal crypts	Intramucosal/superficial invasive cancer	Neoplastic	Endoscopic resection
IV	Branch-like or gyrus-like crypts	Adenoma	Neoplastic	Endoscopic resection
Vi	Irregular crypts	Superficial invasive/deep invasive cancer	Neoplastic	Surgery/endoscopic resection in selected cases
Vn	Non-structural crypts	Deep submucosal invasive cancer	Neoplastic	Surgery

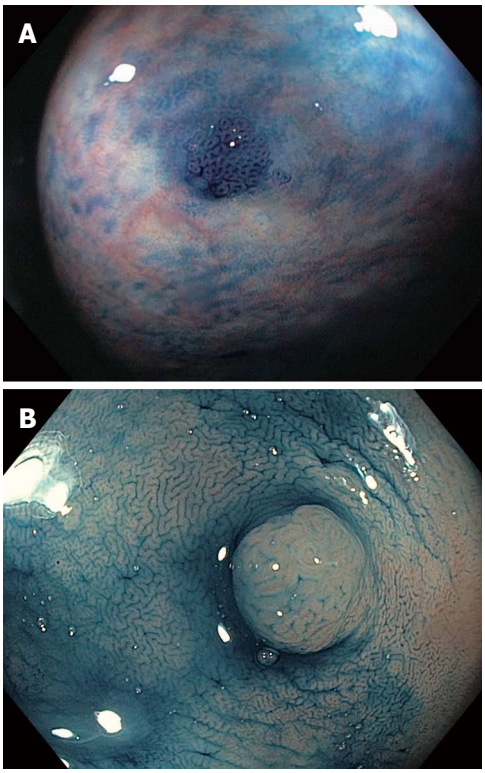

Figure 3 High-resolution endoscopic images of indigo carmine staining for Kudo's pit pattern classification. A: Type II diminutive rectal hyperplastic polyp; B: Type IIIL tubular adenoma with low-grade dysplasia.

in the literature for the assessment of NBI technology. One report evaluating the use of NBI without magnification classified results using a confidence measure, with an observation of at least one histological characteristic designated as a "high confidence" diagnosis prediction, and a "low confidence" prediction indicating there were questionable traits or features belonging to both neoplastic and non-neoplastic categories[28]. The determination of diagnostic predictions with high confidence allows therapeutic decisions to be made at the time of endoscopy. A classification based on capillary pattern (CP) has been introduced by Sano *et al*[29] for use with magnification endoscopes (Table 2, Figure 6). This classification method has demonstrated reliable discrimination of category CP I (non-neoplastic lesions), with correct classification

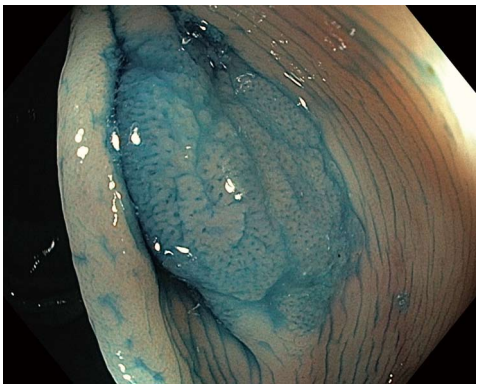

Figure 4 Sessile serrated adenoma type II-O.

of 95.3% of lesions[30]. Application of Sano's classification without the use of magnification yields reduced but satisfactory accuracy (91%)[31]. Similar accuracies have also been reported by studies directly comparing the performance of NBI against CE to distinguish non-neoplastic from neoplastic lesions[19,21,32,33].

Recently, a study using high-resolution white-light images and NBI described several characteristic features of SSA, including a cloud-like surface, indistinct borders, irregular shape, and dark spots within the crypts. The presence of all these features was sufficient to distinguish SSA from HP with an accuracy of 93%[34]. Moreover, the ability to estimate the degree of invasion of colorectal neoplasms with NBI has also been assessed, largely in Asian studies using magnification with a focus on microvasculature characteristics. Application of Sano's classification allowed for the discrimination of cancerous lesions with superficial submucosal invasion (sm1) from those with deeper invasion with an accuracy of 87.7% (sensitivity 84.8% and specificity 88.7%)[35], though accuracy obtained by CE with magnification is superior (98.8%)[11]. Hence, CE with magnification is preferred in cases with suspected invasive lesions.

Since the use of magnification is not widespread, a joint classification with Asian and Western endoscopists has been recently designed. NICE classification (NBI International Colorectal Endoscopic Classification)[36] is based on polyp color as well as surface and vessel patterns (Table 3, Figure 7). Although these features are best

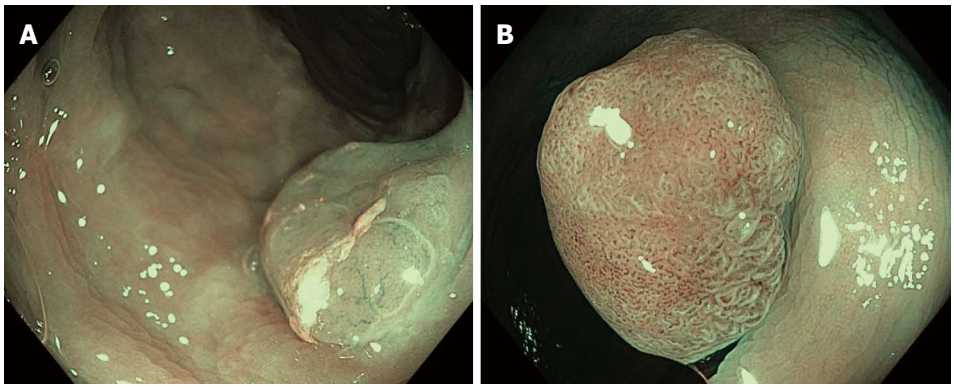

Figure 5 High-resolution endoscopic image of narrow band imaging. A: Hyperplastic polyp with weak vascular pattern intensity and type Ⅱ Kudo's pit pattern classification; B: Tubular adenoma with foci of high grade dysplasia exhibiting strong vascular pattern intensity and type ⅢL Kudo's pit pattern classification.

Table 2 Capillary pattern classification determined from narrow band imaging with magnification

	Sano *et al*[29] classification			
	CP Ⅰ	CP Ⅱ	CP ⅢA	CP ⅢB
Capillary pattern	Absent	Present	Present Meshed capillary vessels with blind endings, branching and curtailed irregularity	
Capillary characteristics	-	Vessels surrounding glands	Lack of uniformity, high density of vessels	Nearly avascular or loose microvessels
Most likely histology	Normal or hyperplastic polyp	Adenoma or intramucosal carcinoma	Superficial submucosal invasive carcinoma (sm1)	Deep submucosal invasive carcinoma
Treatment	None	Polypectomy or endoscopic mucosal resection	Polypectomy or endoscopic mucosal resection/surgery	Surgery

visualized with magnification, NICE categorization is still feasible without it, as preliminary studies differentiated Type 1 from Type 2 in polyps < 1 cm with a sensitivity of 98% and negative predictive value of 95%[37].

The characterization of lesions with NBI has been applied in clinical practice using a "Resect and Discard" concept[38]. Histological analysis and endoscopic resection can be avoided under certain conditions with this strategy, such as in cases with HPs smaller than 5 mm in the rectum and sigmoid. Furthermore, lesions with low carcinogenic potential (adenomas less than 10 mm) can be safely removed and discarded also without a need for histopathological analysis. In both cases, prediction of histology needs to be done with a high degree of confidence, and lesions greater than 10 mm should routinely be sent for histology. This strategy also allows for the establishment of a proper surveillance interval immediately following the colonoscopy, without a need to wait for the pathology report. Initial evaluations of this strategy demonstrated predictions with a high degree of confidence in 89% of polyps and allocation of proper surveillance intervals in 98% of cases[38].

It has been estimated that application of this strategy in the United States would save $33 million dollars annually[39]. The American Association of Gastrointestinal Endoscopy (ASGE) has subsequently stated that polyps ⩽ 5 mm can safely be resected and discarded only after an optical diagnosis with a high degree of confidence has been performed. To determine if these smaller lesions in the sigmoid colon or rectum can be safely left *in situ*, optical diagnostic methods should provide a negative predictive value (NPV) for the diagnosis of adenoma of at least 90%. Moreover, in combination with routine histology of polyps > 5 mm, proper surveillance intervals should be achieved in at least 90% of cases[40]. NBI achieves these requirements when performed by proficient endoscopists, with one recent study demonstrating proper surveillance intervals in polyps ⩽ 5 mm in 92%-99% of cases (according to American or European guidelines, respectively), and a 92% NPV for the diagnosis of rectosigmoid adenomas[41]. However, this threshold was not reached when performed by non-academic centers or non-tertiary hospitals[42-44]. Therefore, NBI interpretation should be applied with caution before making these results generalizable in clinical practice. Furthermore, the medicolegal consequences of the "Resect and Discard" strategy must be taken into account. While the resection and pathologic assessment of low risk lesions carries a huge time and cost burden, advanced histological features (*i.e.*, villous component, high grade dysplasia, or cancer), though rare, can occur in lesions < 1 cm[45]. The guidelines of endoscopy societies should therefore provide legal standards and include recommendations regarding advanced imaging interpretation to support endoscopists. In this regard, it has been proposed that high quality pictures of discarded and un-resected lesions should be included in the endoscopic report[46].

Alternative digital CE techniques, such FICE and

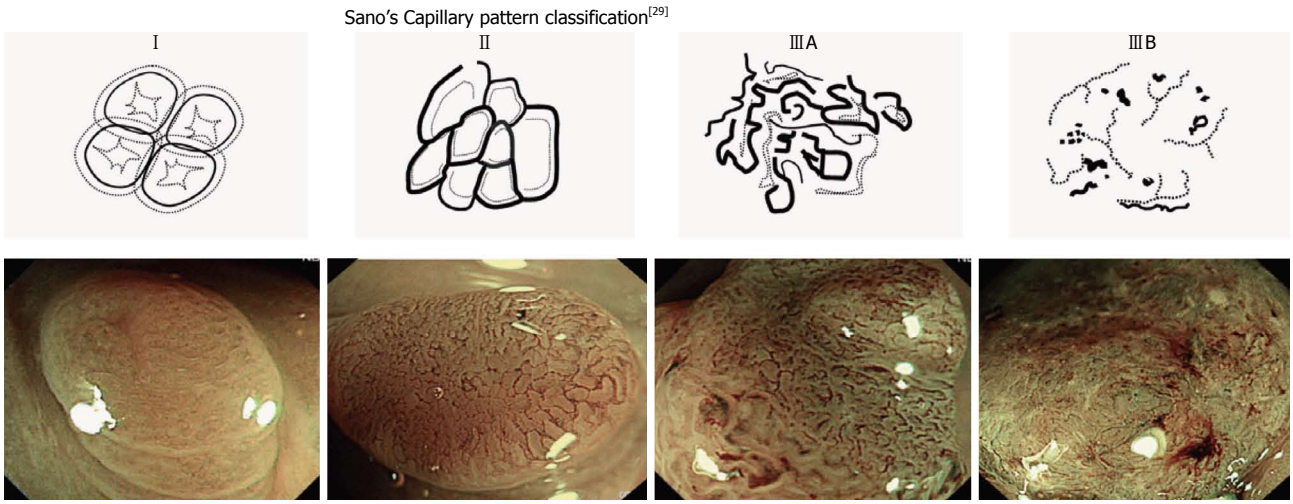

Figure 6 Sano's capillary vessel classification. Adapted from Uraoka *et al*[29].

Table 3 Narrow band imaging-international colorectal endoscopic classification as determined by narrow band imaging with/without magnification

	Type 1	Type 2	Type 3
Color	Same or lighter than background	Brown	Brown or dark brown Occasional white patchy areas
Vessels	None or isolated lacy vessels	Brown vessels surrounding white structures	Areas 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 histology	Hyperplastic polyp	Adenoma or intramucosal or superficial submucosal invasive carcinoma (sm1)	Deep submucosal invasive carcinoma
Treatment	None	Polypectomy or endoscopic mucosal resection	Surgery

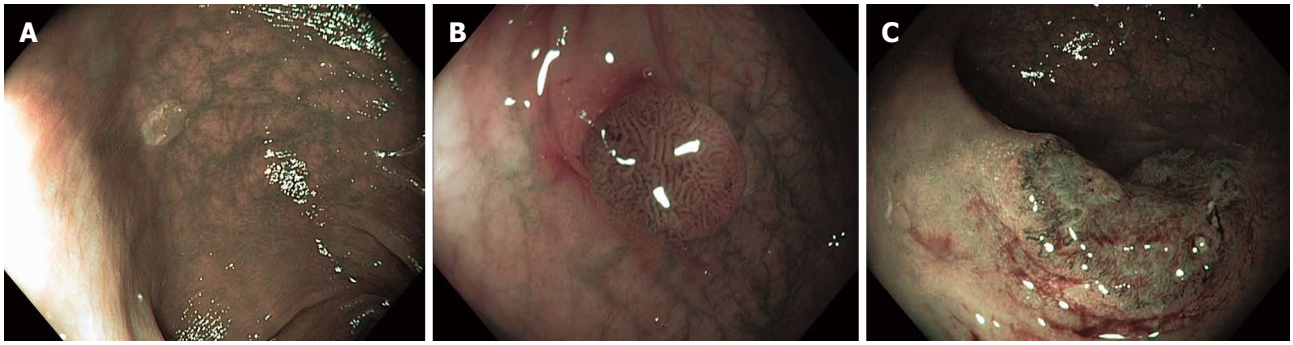

Figure 7 Narrow band imaging-international colorectal endoscopic classification. A: Hyperplastic polyp, narrow band imaging-international colorectal endoscopic (NICE) Type 1; B: Tubular adenoma with low-grade dysplasia, NICE Type 2; C: Deep invasive cancer, NICE Type 3.

i-Scan, have not been as widely implemented as NBI, thus less evidence is available for evaluation and comparison. As FICE and i-SCAN enhance vascularization (with additional selectable modes in which the surface structure is also enhanced), studies to date have been based on inspection of the vascular pattern and/or pit pattern. FICE[47-53] and i-Scan[54-59] systems have been evaluated for the discrimination of neoplastic and non-neoplastic lesions, demonstrating similar results to NBI, although poorer than CE in some cases. FICE combined with magnification has also been tested for prediction of submucosal invasion depth, with accuracies similar to NBI, but significantly lower than CE[51].

CONCLUSION

The exponential increase in lesions detected in the bowel after the implementation of colorectal cancer screening programs along with the improvements in image quality have made the endoscopic characterization of polyps especially relevant. A rigorous estimation of the histologic lesion type facilitates the determination of appropriate endoscopic treatment, if needed, or to indicate surgery. The development of ancillary techniques to white-light endoscopy like CE has enabled accurate discrimination between neoplastic and non-neoplastic lesions along with an estimation of the degree of invasion when combined

with magnification systems. Nevertheless, this technique has not been fully implemented in Western countries since it is cumbersome and time-consuming. Digital CE systems, such as NBI, have attempted to overcome these drawbacks with their ease of use, reversibility and cleanliness. Their capability to accurately distinguish non-neoplastic from neoplastic lesions has been demonstrated, though their use in estimating the degree of invasion still needs further evaluation. NBI, along with the "Resect and Discard" strategy, has proven to be accurate in academic centers and tertiary hospitals, with the potential for significant financial savings. The available evidence suggests that conventional CE is the most accurate technique for the characterization of colonic polyps, though NBI is a viable alternative for experienced endoscopists. Furthermore, inclusion of recommendations regarding advanced imaging interpretation in endoscopy society guidelines will minimize legal consequences of the "Resect and Discard" strategy.

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