

## **Endoscopic Submucosal Dissection for Nonpolypoid Colorectal Dysplasia in Patients With IBD – A Pathway To Further Implement SCENIC**

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The implementation of the Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in Inflammatory Bowel Disease (IBD) Patients: International Consensus Recommendations (SCENIC)(1) is underway. The recommendations are being incorporated into practice.(2) Chromoendoscopy and targeted biopsy technique continues to be disseminated in gastroenterology meetings. SCENIC publications are well referenced. Its classification of superficial dysplasia (Figure 1) is used in many newly published studies, replacing the terms dysplasia associated mass or lesion, adenoma like and non-adenoma like.(3) An image atlas (4) as well as videos of how to perform chromoendoscopy and targeted biopsy (5, 6) are freely available.

In this issue of the Journal, we are particularly pleased that Kinoshita and colleagues fill, in part, the gap in literature on the potentials of endoscopic resection in the management of Nonpolypoid Colorectal Dysplasia (NP-CRD). Their publication is needed for the full implementation of SCENIC.(7) While SCENIC recommendations include the following statement: “After complete removal of endoscopically resectable nonpolypoid dysplastic lesions, surveillance colonoscopy is suggested rather than colectomy,” the authors of SCENIC recognized that the quality of evidence was very-low. In addition, they were cognizant that NP-CRD could confer a higher colorectal cancer (CRC) risk and removal of NP-CRD could be more technically difficult, requiring endoscopic mucosal resection or endoscopic submucosal dissection (ESD).(8, 9)

The detection of NP-CRD is the first step in the prevention of CRC in patients with IBD. Thus, these lesions must be detected early and completely, and preferably, are

amenable to endoscopic resection.(10) To achieve early detection, we need the right mindset; a mindset that is open to the idea that NP-CRDs can occur in all colonic IBD patients and that chromoendoscopy enhances the yield to detect them. For example, twenty percent of Kinoshita and colleagues' patients had disease limited to the left colon. They also had a widely variable length of colitis.

In the context of detecting NP-CRD, the indigo carmine and methylene blue dyes function as contrast agents, which enhance the appearance of the lesions (Figure 2). The dye highlights the border of the lesion by pooling at its periphery. In addition, the dye fills the innominate grooves (the fine mucosal creases) of the colon mucosa. Because NP-CRD lesions interrupt the innominate grooves, its border of NP-CRD can be traced to where the grooves suddenly end. The dye makes the morphology of the lesion to stand out by pooling into depression or ulceration.(11)

The differential presence of the dye on the NP-CRD as compared to the surrounding tissue allows us to visualize the lesion itself (Figure 3). The NP-CRD appears more red while the surrounding is bluer. This phenomenon, which we call “red in blue” sign, probably occurs because dysplasia often has shallower and narrower glands. In addition, it is likely that the slight elevation contributes to the lesion having less dye on its surface. While we use it in our practice, at present, unfortunately, the sensitivity and specificity of this “red in blue” sign has not been described.

In this editorial, we have collated our opinions on the different endoscopic findings that should be sought during chromoendoscopy (Table 1) to facilitate the identification of NP-CRD (Figure 4). We based our observations by Kudo and colleagues (12). Areas containing these findings should be investigated in detail, and if a lesion has been identified, a more concentrated dye solution can be sprayed onto the lesion in order to evaluate its surface pattern. Targeted biopsy should be directed towards the area in question or the lesion, although when resources and expertise are available and the lesion is deemed low grade or serrated, resections may be performed in the same setting. Alternatively, with high quality photo documentation, the location of the lesion may be marked with submucosal injection of India ink away from the lesion. Then the resection is performed at a later date.

Historically, detailed analysis of the pit-pattern of colorectal lesions using chromoendoscopy and interpretation of lesion histology has been based on the Kudo classification.(12) The criteria were developed primarily from observations of surface pattern in non-colitic colorectal lesions. However, colorectal lesions in patients with IBD have proved a challenge to interpret. Kinoshita and others, showed that applying the Kudo classification in the evaluation of NP-CRD in patients with IBD was as good as a coin flip in predicting low-grade dysplasia, (i.e. approximately one half of lesions they diagnosed by endoscopy to be low grade were actually high grade dysplasia or cancer).(4) A recent image analysis study of the Kudo classification system with chromoendoscopy showed that the overall interobserver agreement by experienced endoscopists for any pit pattern was only fair ( $k=0.282$ ). In fact, the classification was

more so useful to generally differentiate between non-neoplastic and neoplastic pit patterns, showing a high negative predictive value of Type I and II to rule out neoplasia (Figure 5).(13) The reasons for the lack of classifiable patterns is unclear, but it may reflect the continuing inflammation and the higher incidence of poorly differentiated and signet ring cancers (14) diagnosed in colonic IBD.

Scarring of the colon from chronic inflammation in colonic IBD imparts the need to perform ESD for sessile and NP-CRD larger than 1 cm, and certainly, more than 2 cm. As shown by Kinoshita et al. and others (Table 2), submucosal fibrosis was found in almost all of their patients. Thus, these lesions were either partially-lifting or completely non-lifting.(7, 15, 16) Endoscopic mucosal resection using the inject-and-cut technique requires lifting and leads to piecemeal resection for lesion larger than 2 cm.(17) In contrast, ESD allows the lesion to be isolated and the underlying fibrotic submucosa to be incised.(18, 19) Therefore, ESD would allow fulfillment of the criteria set forth by SCENIC, which specifies that to be endoscopically resectable these lesions must fulfill the following criteria: “(1) distinct margins of the lesion could be identified, (2) the lesion appears to be completely removed on visual inspection after endoscopic resection, (3) histologic examination of the resected specimen is consistent with complete removal, and (4) biopsy specimens taken from mucosa immediately adjacent to the resection site are free of dysplasia on histologic examination.”

It is notable that despite the fact that while ESD experts performed the resections, curative resections were achieved only in approximately 80% of the cases from the

three series and that they were incomplete because of positive vertical margin. These data emphasize further that large NP-CRD ought to be cut en-bloc as piecemeal removals could lead to difficulty in assessing the vertical margin and to recurrence (which may be invasive or even metastatic cancer).

The need for ESD to remove large sessile and NP-CRD poses a major problem to patients with colonic IBD in many Western countries because ESD has not become universally available. There are, however, reasons to be optimistic. Recent studies have shown that Western endoscopists are able to perform the procedure despite the lack of opportunity to perform it in a large number of patients with early gastric cancers. These studies,(20, 21) albeit in Barrett's neoplasia, reverse many prior negative studies.

Additionally, the accessories needed to perform ESD are now as available in the US and Europe as they were in Japan. A major issue that has not been resolved in the US, however, is the lack of the appropriate reimbursement for ESD. In contrast, ESD is reimbursed by the National Health Insurance, in Japan, as long as it is indicated, which includes the resection of NP-CRD.(22) Without the appropriate CPT code and reimbursement, it seems unlikely that the availability of ESD can be scaled up to many IBD centers throughout the US.

The Hybrid-ESD/Simplified-ESD technique (23) has the potential for use while the issue of reimbursement is (hopefully) addressed by our professional gastroenterology and gastrointestinal endoscopy societies (Figure 6). The technique can be a bridge between EMR and full ESD (Figure 7) although the technique is applicable for only lesions up to

3 to 4 cm. In the Hybrid-ESD/Simplified-ESD, after circumferential incision and minimal submucosal dissection, lesions are resected using a snare. In contrast, in the full ESD technique, the submucosa under the lesion was dissected in its entirety. In our experience, we use saline submucosal injection in order to achieve a partial lift. Others use hyaluronate. A circumferential incision is then made and the lesion is subsequently removed using a snare. The procedure, when applied to cut lesions with median of about 26 mm, requires approximately 27 minutes. Note however that the complication rates of the Simplified-ESD had been reported to be similar to those of Full-ESD (Figure 7).(24) However, most complications of ESD are now treated endoscopically.

In summary, chromoendoscopy with targeted biopsy is the current standard to detect and diagnose dysplasia. As we find more dysplasia, we recognize its challenge to endoscopically resect, especially NP-CRD. Kinoshita and colleagues, and others, showed the potential of ESD to resect NP-CRD safely and effectively. Moreover, limited summary data from the three available studies (7, 15, 16) showed no local or metachronous cancer, but a high risk for subsequent NP-CRD (5.6 metachronous dysplastic lesions per 100 years patient follow up) (Table 3). This rate is similar to rates of metachronous dysplasia reported after resection of polypoid dysplasia (6.5 cases per 100 patient years, 95% CI: 5.4-7.8).(25) However, follow up was only short- to medium-term (27 months). Thus, though promising, confirmation from prospective studies will further support that ESD is safe and effective to resect NP-CRD. In the meantime, we need to care for these high risk patients, and, optimize the endoscopic management using ESD when appropriate to resect NP-CRD. Based on our experience in performing



ESD for NP-CRD, we have collaboratively put together a list of suggested indications (Table 4).

## Figure Legend

**Figure 1.** SCENIC endoscopic classification of superficial colorectal dysplasia in patients with inflammatory bowel disease. The classification is a modification of the Paris endoscopic classification of superficial neoplastic lesions. The modifications included the addition of terms (presence or absence) to describe ulceration and border of the lesion. The SCENIC classification replaces the terms dysplasia-associated lesion or mass (DALM) and adenoma like and non-adenoma like. Note that, in patients with IBD, the nonpolypoid colorectal dysplasia in IBD is often completely flat (or the same level) as compared to the surrounding mucosa. This is different from patients without IBD who rarely have a completely flat dysplasia. Thus, in patients without IBD “flat lesion” is colloquially used to describe lesions that are slightly (superficial) elevated as compared to the surrounding mucosa. Descriptions of the terms are listed (modified from Ref (3, 8)).

**Figure 2.** Preparation and application of chromoendoscopy for detection and detailed inspection of nonpolypoid colorectal dysplasia in patients with inflammatory bowel disease. Detection: A. A light color is used for detection of dysplasia B. Mix dye agent\* with 250ml of water. C. Use the water accessory foot pump to apply the chromoendoscopy solution. Detailed Viewing: D. A darker color is used for detailed viewing of dysplasia. E. Mix dye agent\*\* with water into a straight tipped 60cc syringe. F. Spray directly through the endoscopy accessory channel using a 60cc syringe

Foot Notes:

## Chromoendoscopy for Detection

### Indigo Carmine:

1. American Regent, Shirley, NY, 5ml (0.8%) - Mix two 5ml ampule (0.8%) with 250 ml of water. The manufacturer's suggested retail price (MSRP) is approximately \$330 (\$165 per 5ml of 0.8% solution).
2. Microtech, Ann Arbor, MI, 5ml (0.4%) - Mix four 5ml ampule (0.4%) with 250 ml of water. The MSRP is approximately \$156.80 (\$ 39.2 per 5 ml of 0.4% solution).

### Methylene Blue:

1. American Regent, Shirley, NY, 10ml (0.5%) - Mix one 10ml ampule (0.5%) with 300ml of water. The MSRP is approximately \$202.69 (\$202.69 per 10ml of 0.5% solution).

## Chromoendoscopy for Detailed Viewing

### Indigo Carmine:

1. American Regent, Shirley, NY, 5ml (0.8%) - Mix one 5ml ampule (0.8%) with 20 ml of water in a 60cc syringe to approximate a 0.16% dilution. The MSRP is approximately \$165 (\$165 per 5ml of 0.8% solution).
2. Microtech, Ann Arbor, MI, 5ml (0.4%) - Mix two 5ml ampule (0.4%) with 15 ml of water in a 60cc syringe to approximate a 0.16% dilution. The MSRP is approximately \$78.60 (\$ 39.2 per 5 ml of 0.4% solution).

### Methylene Blue:

1. American Regent, Shirley, NY, 10ml (0.5%) - Mix one 10ml ampule (0.5%) with 20ml of water in a 60cc syringe to approximate a 0.16% dilution. The MSRP is approximately \$202.69 (\$202.69 per 10ml of 0.5% solution).

**Figure 3.** The Red in Blue sign – the lesion, which appears red, is in a blue surrounding. One way the dye improves our visualization of a flat lesion is by making some lesions appear more red than the surrounding. These observations are derived from the detection of early gastric cancer. A, there was a spontaneous bleeding on white light. B, After dye spraying, a large superficial elevated lesion could be appreciated. C, Closer view of the lesion. D, Similar to Kinoshita et al, the dye helped to determine the margin of the lesion for ESD. E, Pathology of the lesion showing dysplasia associated colitic and horizontal or vertical margin free of dysplasia. F, Artist rendition of the phenomena seen: dysplasias often have shallower and narrower glands, and there was a slight elevation of the lesion. These reasons were likely to have contributed to the lesion having less dye on its surface. The sensitivity and specificity of this sign is not known at present.

**Figure 4.** Examples of lesions exhibiting signs of NP-CRD during chromoendoscopy examination.

**Figure 5.** The pit-patterns of NP-CRD. Detailed evaluation of the pit-pattern can be complex and tedious. It requires magnification. There are also many patterns that

require a significant learning. In patients with IBD, in general, we need to focus only on a few general patterns: Type 1 (normal mucosa), Type 2 (hyperplastic tissue), NP-CRD, and Type VN (invasive cancer). Note that patterns for sessile serrated adenoma is not included.

**Figure 6.** Simplified-ESD/Hybrid-ESD. A patient with long-standing colonic IBD was referred after chromoendoscopy with targeted biopsy of a 2 cm flat lesion in the rectosigmoid colon showed low grade dysplasia. A, The lesion, a 1.7 cm NP-CRD, superficial elevated (flat), viewed with chromoendoscopy. B, The border of the lesion was marked with brief bursts of cautery. The Dual knife (Olympus Corp) was used. C, After injection with saline mixed with indigo carmine, a circumferential incision was made around the lesion. The lesion was completely isolated from its lateral surroundings. D, Under water viewing of the submucosa below the lesion showing severe fibrosis. The lesion was on top part of the image and the muscle layer, which was white, was at the lower part. E, The lesion was captured using a stiff snare. The stiff snare was closed completely to the hub prior to applying cautery in order to prevent entrapment of the muscularis mucosa. F, Exposed submucosa and muscularis propria after en-bloc resection. The pathology was low grade dysplasia.

Figure 7. An example of Full ESD to remove a large NP-CRD. A, A large dysplasia was seen between 6 to 12 o'clock position. The periphery of the lesion had been marked. After circumferential marking for the margin of an NP-CRD; B, the submucosa was carefully dissected with Flash Knife coupled with Sumitomo Bakelite Knife. Severe

fibrosis could be appreciated; C, Minor bleeding was encountered frequently during the dissection; D, The lesion had been completely removed en-bloc resection.

## Tables

Table 1. Described signs of NP-CRD during colonoscopy\*

Sign	Description
Interruption of Innominate Grooves	Grooves in the colonic mucosa that become less pronounced with luminal distention. The grooves are absent in neoplastic process.
Wall deformity Slight elevation Slight depression Nodularity	Discontinuation of the expected contour Convergence or distortion of smooth line of haustral folds Expansion of fold
Spontaneous friability	The area may bleed before the endoscope, which was not due to endoscope trauma, but may occur with vigorous washing
Shallow ulcer	Ulcerations may be present because of disease activity or neoplastic process
Velvety appearance/ Villous mucosa	Sulcus/gyrus like pattern, sometimes with a clearly villous component. Clear breaks in innominate grooves
Slight discoloration	Typically, slightly more reddish But, may also be more whittish
Red in blue	The lesion appears red and the surrounding appears blue (see Figure 2)

- As of December 2017

Table 2. Summary of recent studies of ESD to resect NP-CRD

	Kinoshita(7)	Suzuki(16)	Iacopini(15)
No of patients (lesions) studied No of center	25 Single center	31 (32) Multicenter (Japan and UK)	9 (10) Multicenter (Italy and Japan)
Patient Selection			
Inclusion			
Number of lesion	Single	Single	Single
Colitis must be in clinical remission	Yes, mild only	Yes, up to moderate	Yes, mild only
Benign to superficial neoplasm	Yes	Yes	Yes
Exclusion			
Invisible or no clear margin	Yes	Yes	Yes
Lesion characterization			
%NPCRD/%Sessile	80/20	81/19	100/0
Method to determine border	Indigo carmine, 100% accurate	Indigo carmine	Perhaps Indigo carmine
Size	> 10 mm	33.5mm range 14-73mm	> 20 mm
Pit-pattern: Low-grade adenoma or superficial cancer versus deeply invasive cancer	Yes		Partly Yes Only at Japanese centers
NBI-pattern: Low-grade adenoma or superficial cancer versus deeply invasive cancer	Yes	Yes	Yes
ESD technique	Yes	Yes	Yes
Expert only	Yes	Yes	Yes



Complications			
Perforation, %	4	0	0
Bleeding, %	0	3	10
Findings			
Submucosal fibrosis seen, %	100	97	90
Adipose deposition seen, %	NA	41	NA
En bloc, %	100	91	80
Curative resection, %	76 24% had positive vertical margin or lymphovascular	79	70
Resection size (means), in mm	34.9±17.1		
Histology, %	T1 8 HGD 44	T1 13 HGD 22	T1 20 HGD 30
Outcomes at follow-up			
Median follow-up, in months	21 (8-80)	33(6-76)	24(6-72)
Recurrence	0	1/26	2/10

Table 3. Rates of metachronous dysplasia after ESD for NP-CRD

Study	Metachronous* dysplasia	Follow up (median)	Pathology and number of lesions
Iacopini	3/8 (38%)	24 months	LGD - 3
Suzuki	3/27 (11%)	33 months	Dysplasia - 3
Kinoshita	1/20 (5%)	21 months	HGD - 1
Summary	7/55  (13%; 95% C.I. 6-25%)	27 Months	

\*defined as further dysplasia occurring away from the ESD resection site

Table 4. Suggested Indications for ESD in NP-CRD

Patient Selection	Age >50-years-old ESD in the younger and healthy patients may not be suitable given of the potential risk for metachronous lesions
	Colonoscopy shows remission to mild activity (Mayo 0 or 1) disease activity.
	Patients with primary sclerosing cholangitis should be considered to have higher risk for colorectal cancer. (26)
Number of lesions	Preferably with single lesion > 10mm
Macroscopic features	Lesion with clearly demarcated border
Surface pattern of lesions NOT suitable for endoscopic resection	Lesion without border Lesion with large depression Lesion with VN surface pattern
Pathology	Low grade to high grade dysplasia
	Sessile serrated adenoma/polyp with/out dysplasia
	Complete removal
	Well differentiated carcinoma with invasion depth less than 1,000µm (in Japan)
	NOT INDICATED: signet cell carcinoma and poorly differentiated carcinoma
Follow-up	Repeat colonoscopy within 6 to 12 months
	Biopsy scar site and surrounding tissue
Team for endoscopic resection of dysplasia in IBD	The management of NP-CRD requires a team approach that comprise not only an experienced endoscopy team, but also gastrointestinal pathologist and IBD surgeon (27).

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