Advanced endoscopic techniques in the assessment of inflammatory bowel disease: new technology, new era

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ABSTRACT
Endoscopic assessment of inflammation and mucosal healing is crucial for appropriate management in IBD. Current definition of endoscopic mucosal healing has been derived using previous generation of standard white light endoscopes. New endoscopy technologies widely available provide much more detailed images of mucosal and vascular patterns. Novel endoscopic techniques with high definition image, optical and digital enhancement have enhanced the quality and fine details of vascular and mucosal pattern so that endoscopic images have started to reflect histological changes for lesions and inflammation/healing. These technologies can now define subtle inflammatory changes and increase detection and characterisation of colonic lesions in patients with IBD. The best endoscopic technique to detect dysplasia in IBD is still debated. Dye chromoendoscopy with targeted biopsies is considered by Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in inflammatory Bowel Disease Patients: International Consensus Recommendations (SCENIC) consensus the standard of care and recommended for adoption by gastroenterologists in practice. In future, it is possible that well-trained colonoscopists using high definition equipment with image enhancements may be able to obtain equivalent yield without pan-colonic dye spraying and characterise lesions. Finally, SCENIC introduced endoscopic resectability of some dysplastic colonic lesions—new techniques may now better characterise endoscopic resectability and limit the number of colectomies. In this review, we will provide a state-of-the-art opinion on the direction of technological advances in the assessment of IBD and how new concepts will refine clinical practice.

INTRODUCTION
Endoscopic assessments of extension, grade of inflammation and mucosal healing (MH) as well as early detection of neoplastic colonic lesions are important key parameters for management of patients with IBD. Indeed, mucosal and histological healing predicts sustained clinical and steroid-free remission, and avoids complications, hospitalisation and surgery. There is an emerging strategy in some countries to consider stopping or de-escalating biological therapy in patients with IBD to reduce side effects and cost burden. Endoscopic MH is a key end point to achieve before considering exit strategy from targeted therapies.1 In general, patients in clinical, biomarker and endoscopic remission are more likely to remain well when treatment is de-escalated. However, there is still not an ideal validated definition of endoscopic MH in IBD. The current endoscopic scoring systems, used in the clinical practice, to assess severity of inflammation in IBD were not designed to reflect endoscopic features of MH. They have some limitations, cannot detect and assess mild patchy inflammatory mucosal changes and differentiate well between quiescent and mild activity of the disease. Importantly, most of these endoscopic scores have been developed with the previous generation standard white light endoscopes (WLE).2 With the new advanced high definition (HD) endoscopic technologies, optical diagnosis narrow band imaging (NBI, Olympus Japan), optical enhancement iSCAN (iSCAN-OE, Pentax, Japan), blue laser image (BILI, Fujifilm, Japan) and confocal laser endomicroscopy (CLE, Mauna Kea, France), endocyteoscopy (Olympus, Japan) and the emerging endoscopic molecular labelling, modern endoscopy can attain optical characterisation reflecting histology better. In Crohn’s disease (CD), the need for a new consensus to define mucosal healing is clearly required as discussed in details as a viewpoint recently by Bossuyt et al.3 It is still debated how surveillance should be optimally performed to increase the detection rate of colonic neoplasia in patients with IBD and better characterise lesions. Dye chromoendoscopy (DCE) is considered the standard endoscopic technique following the SCENIC consensus statements. While DCE with targeted biopsies currently provides the best lesion detection yield in long-standing UC, there is growing evidence that in future well-trained colonoscopists using HD equipment with optical and digital enhancements may be able to obtain equivalent yield without pan-colonic dye spraying.4 We discuss below how such new techniques, combined with new endoscopic advanced endoscopic resection techniques (mucosal and submucosal resection) promises to limit the number of colectomies in the presence of dysplasia.

We have not considered small bowel enteroscopy or video capsule enteroscopy in this review where advanced imaging technologies have not been widely applied. We have not discussed advanced therapeutic procedures such as dilation of strictures but these have been discussed in recent references.6
CURRENT STATUS OF ENDOSCOPIC AND HISTOLOGICAL HEALING IN UC AND CD
MH is an important therapeutic end point to achieve in IBD and is now widely accepted as a reliable target for optimum management of patients with IBD (selecting therapeutic targets in inflammatory bowel disease (STRIDE)). The terms MH and ‘deep remission’ (clinical+endoscopic) are considered new therapeutic targets in the treatment of patients with IBD. MH is a term used interchangeably with endoscopic healing, although in future these two terms may become more specific.

At present, there is no clear endoscopic definition of MH when WLE is used, and the lower end of endoscopic inflammation assessment scale is considered de facto MH. In the clinical trials, Mayo endoscopic score (MES) 0 and 1 are considered to represent MH, but 0 is better than 1 and should be the optimal goal to aim for.8–11 Carvalho et al reported that in patients with left-sided or extensive colitis, MES 1 was associated with an increased risk of clinical relapse compared with MES 0 (27.3% vs 11.5%, p=0.022) as well as increased risk of steroids or immunosuppressant drugs and hospitalisation (13.0% vs 3.3%, p=0.044). Clearly, using MES 1 has limitations when considering MH.8

The time period for observation was at 12 months after total colectomy. The exact histological definition of MH continues to evolve yet to be determined and currently is not considered as a target in UC (STRIDE).12 However, histological assessment in addition to HD white light colonoscopy is considered a sensitive measure of the absence of inflammation and there are evolving histological classifications being developed such as Robarts Histological Index (RHI) and Nancy Histological Score that aim to better define remission.13

### Current endoscopic scoring systems in UC and their limitations

Several scoring systems have been developed using WLE, some of which require further validation and none of these included the specific endoscopic features and definition of MH. MES is the most commonly used in the clinical practice and trials and more recently other scoring systems have been developed and validated such as the Ulcerative Colitis Endoscopic Index Severity (UCEIS) and The Ulcerative Colitis Colonoscopic Index of Severity (UCCIS)13–14 (table 1).

Travis et al proposed the UCEIS based on WLE as a reliable and validated score of endoscopic severity in UC as an alternative to the MES.13 UCEIS takes into account three endoscopic findings—vascular pattern, bleeding and erosions/ulcers. It is a useful tool in clinical practice and is starting to be adopted routinely in central readouts for clinical trials. However, it also has several limitations as the definition of MH and the threshold for mild

### Table 1  Endoscopic scoring systems in UC using WLE and VCE

| Endoscopic scores | Endoscopic technique | Endoscopic findings | Validation | Pros | Cons |
|-------------------|----------------------|---------------------|------------|------|------|
| Mayo endoscopy subscore13 | WLE | Vascular pattern, erythema, friability, erosions and ulceration, bleeding | Partially validated | Easy to use | No endoscopic definition of MH overlap grade 1–2; subjective elements |
| Ulcerative Colitis Endoscopic Index of Severity14–15 | WLE | Vascular pattern (three levels), bleeding (four levels), ulceration (four levels) | Validated | Easy to use | No endoscopic definition of MH |
| Ulcerative Colitis Colonoscopic Index of Severity14–15 | WLE | Vascular pattern, granularity, lesions, friability/bleeding | Partially validated | Easy to use | Requires total colonoscopy |
| Modified Mayo endoscopic score16 | WLE | Vascular pattern, granularity, friability, bleeding, ulceration | Not validated | Easy to use | No established thresholds for mild, moderate and severe disease |
| Magnifying Colonoscopy UC grade17 | NBI+magnification | Grade 1: pits small, round and regularly arranged Grade2: pits rather large, oval and somewhat irregular in arrangement Grade3: pits of various shapes and sizes and irregularly arranged Grade4: dispersed pits varying in morphology, associated with the presence of small erosion | Not validated | Endoscopic definition of MH | Difficult to be adopted in clinical practice |
| Paddington International Virtual ChromoendoScopy ScOre18 | VCE-iSCAN | See table 2 | Partially validated | Definition of mucosal and vascular MH Correlate with histological healing | Requires endoscopy experience |
| LCI20 | LASEREO LCI | LCI vascular patterns A, no redness; B, redness with visible vessels and C, redness without visible vessels | No validated | Definition of vascular healing Endoscopic definition of MH | Difficult to be adopted in clinical practice |

LCI, linked colour imaging; MH, mucosal healing; NBI, narrow band imaging; VCE, virtual chromoendoscopy; WLE, white light endoscopy.
to moderate and severe disease are not clearly described, the disease extension is not evaluated and advantage in the interobserver agreement over MES has not yet been demonstrated.

The UCCIS was recently proposed to overcome these limitations and to include disease extension but is more complex, has not been adopted in daily practice and is not validated in large studies yet.16

Some of the components of these scores such as vascular pattern are now outdated as newer generation of endoscopes demonstrate abnormal vascular patterns rather than loss or obliterated vascular pattern and friability, in severe disease as well as in mild disease.15 16 Regenerative changes and scarring/drop out of pits have generally not been considered with WLE. Therefore, there is a need for new or adapted endoscopic scoring systems that are relevant to the current generation of HD endoscopes equipped with electronic virtual chromoendoscopy (VCE).

**Current endoscopic scoring systems in Crohn’s disease and their limitations**

In CD, the inflammation is transmural and MH is considered as minimum goal for successful mucosal end point (STRIDE).7 The assessment of inflammation in CD requires multiple cross-sectional radiological imaging (MR or CT enterography, preferably the former) and/or mucosal endoscopic evaluation to ensure complete healing after therapy (including enteroscopy).

The most common endoscopic scoring indices are the CD Endoscopic Index of Severity (CDEIS) and the Simple Endoscopic Score for CD (SES-CD).18 19 However, the operating characteristics in terms of validation, responsiveness and reliability of these endoscopic indices to assess inflammation and predict outcome in CD is not clear yet. Potential limitations of these endoscopic scores are that these do not include the definition of MH, and the complexity of calculation make these score difficult to be adopted in daily clinical practice. Recently, Khanna et al have also assessed the responsiveness of the CDEIS and SES-CD using data from a trial of adalimumab. The SES-CD demonstrated numerically greater response to treatment and compared with CDEIS, stronger correlation with the global evaluation of lesion severity, and is less cumbersome to calculate.20 However, the exact threshold of SES-CD to define response to therapy as endoscopic end point in clinical trials, the general lack of clear definition of MH and of adoption in clinical practice remain limitations.

The Rutgeerts score for postoperative CD recurrence was developed in 1990 by examining 89 patients with ileal resection for CD and observing clinical outcomes in patients with early neo-terminal ileum lesions. A 5-grade stepwise numeric ulcers index gradation of endoscopic postoperative recurrence in the neo-terminal ileum were developed.21 Although the score has been adopted in both trials and clinical practice, only a few very recent studies have explored intraobserver and interobserver agreement, but lack robust formal validation. Another limitation of the Rutgeerts score is when the anastomosis cannot be reached and passed, the neo-terminal ileum cannot be assessed. Clear distinction between inflammatory and suture or ischaemic ulcers is difficult. Further new development and more detailed scoring systems are required in the future, especially as all the scores were defined using WLE only.11

**WHAT ARE THE NEW TECHNOLOGIES THAT ARE AVAILABLE**

Recent advances in endoscopic assessment in IBD include DCE, VCE, CLE and endocytoscopy which have dramatically improved visualisation of patchy subtle mucosal changes allowing targeted biopsies and increasing the yield and characterisation of colonic dysplastic lesions in IBD. In addition, the image resolution of HD endoscopes is much improved compared with standard WLE. Thus, novel endoscope have started to show promise to approximate histological readouts.21

**High definition and dye chromoendoscopy**

HD colonoscopy is an advanced technology employing an HD monitor and high-resolution charge-coupled device. HD endoscopes produce image signals with resolution of 850 000–2 million pixels and offer a field of vision of 170°, instead of standard definition (SD), which produces signal images with resolutions of 100 000–400 000 pixels with a field of vision of 130°.

The increased resolution of HD endoscope offers an opportunity for better characterisation and definition of the borders of neoplastic lesions in patients with IBD.22 DCE is an endoscopic technique which uses the topical application of stains to improve identification and characterisation of colonic lesions during endoscopy. Common staining agents used are methylene blue as an absorptive contrast and indigo carmine as a reactive agent.23

**Dyeless chromoendoscopy**

VCE includes optical technologies such as NBI, flexible imaging colour enhancement (FICE, Fujinon) and iSCAN (Pentax) and can enhance details of tissue surface without any application of dye, as well as blood vessels. A direct image is obtained with the standard WLE, which uses the full visible wavelength range (400–700 nm) to produce a red-green-blue image, and with NBI, where optical filters are used to reflect the light. FICE and iSCAN methods are based on the reflection of photons to reconstruct virtual images, through a digital postprocessing of the endoscopic images, without any filter application.24–27 Two new image-enhanced colonoscopes, using the LASEREO system (Fujifilm, Japan), have recently been developed: BLI and linked colour imaging (LCI). The BLI system is equipped with a light source (LL-4450) and a processor (VP-4450HD) with two types of diode laser and it can be used for the examination of both the microvessels and the mucosa.

The LCI expanded the colour range of reddish and whitish colours, therefore enhancing slight differences in the red region of the mucosa in conditions including inflammation and cancer.27 The new iSCAN-OE (Pentax) is a combination of optical and a digital enhancement chromoendoscopy in a single system. It consists of three different algorithms that can be selected...
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Video 1  Endoscopic findings using new technologies- first NBI with and without near focus (mild UC) followed by iSCAN Optical Enhancement with and without magnification (mild UC); for comparison we have presented NBI with and without near focus (quiescent UC) followed by iSCAN Optical Enhancement with and without magnification (quiescent UC).

by pressing a button on the endoscope: contrast enhancement (to digitally add blue colour to relatively dark areas), surface enhancement (to modify luminance intensity) and tone enhancement.26

A novel endoscopic system and colonoscope with NBI capability and a ‘dual focus’ function has recently been introduced. This enables dual focus near-field magnification by pushing a single button to closely examine the mucosal tissue and capillary network.27 Currently, many gastroenterologists are not using the full potential of such advanced technologies integrated in current generation of equipment.

APPLICATIONS OF NEW TECHNOLOGIES THAT ARE AVAILABLE IN IBD

New paradigms to assess endoscopic inflammation and healing in IBD

Recently, many studies have showed that HD in combination with VCE can precisely assess inflammatory activity and extension of IBD disease.10 28–34 With the advanced VCE systems the vessels appear not absent or obliterated but irregular and distorted, especially in mild and patchy inflammation.

First, Kudo et al have showed that NBI can contribute to the clear visualisation of mucosal vascular pattern (MVP) in patient with UC.27 They have showed MVP to be associated with the histological severity, especially regarding acute inflammation in patients with UC. NBI could depict vessels in the deep layer, which could not be discerned by SD-WLE. The MVP under NBI comprises two distinctive patterns: deep vasculature as depicted green in colour, and superficial vasculature which are brown in colour. There was a significant association with acute inflammatory cells (26% vs 0%, p=0.0001) and goblet cell deposition (32% vs 5%, p=0.0006) in the segments with distorted MVP. However, NBI has some limitations to assess moderate/severe disease where intramucosal bleeding is a feature due to the absorption of light by haemoglobin, but there maybe a role in predicting relapse in patients with quiescent disease.29 30 Hayashi

| Table 3  Detection rate of dysplasia in studies comparing DCE vs VCE or HD |
|----------|----------------|----------------|----------------|----------------|----------------|
| Study    | Year  | Type of study | Type of endoscopy | No. of patients | Dysplasia |
| Kiesslich et al | 2003 | Randomised | DCE vs WLE | 165 | DCE | 35 | HD | 11 |
| Rutter et al | 2004 | Non-randomised | DCE vs WLE | 100 | NBI | 9 | HD | 2 |
| Marion et al | 2008 | Non-randomised | DCE vs WLE | 102 | NBI | 22 | HD | 16 |
| Picco et al | 2013 | Non-randomised | NBI vs HD | 75 | NBI | 22 | HD | 10 |
| Carballal et al | 2018 | Non-randomised | DCE vs VLE vs HD | 350 | NBI | 94 | HD | 27 |

| Study    | Year  | Type of study | Type of endoscopy | No. of patients | Dysplasia |
| Dekker et al | 2007 | Non-randomised | NBI vs WLE | 42 | NBI | 9 | DCE | 13 |
| van den Broek et al | 2011 | Non-randomised | NBI vs HD | 48 | NBI | 13 | DCE | 11 |
| Ignjatovic et al | 2012 | Randomised | NBI vs WLE | 112 | NBI | 5 | DCE | 7 |
| Leifeld et al | 2015 | NBI vs HD | NBI vs HD | 159 | NBI | 31 | DCE | 30 |

| Study    | Year  | Type of study | Type of endoscopy | No. of patients | Dysplasia |
| Pellise et al | 2011 | Randomised | NBI vs DCE | 60 | DCE | 10 | HD | 12 |
| Bisschops et al | 2018 | Randomised | NBI vs DCE | 131 | DCE | 22 | HD | 31 |
| Efthymiou et al | 2013 | Non-randomised | NBI vs DCE | 44 | NBI | 23 | DCE | 27 |

| Study    | Year  | Type of study | Type of endoscopy | No. of patients | Dysplasia |
| Iacucci et al | 2018 | Randomised | iSCAN vs DCE vs HD | 270 | iSCAN | 23 | DCE | 27 |

DCE, dye chromoendoscopy; HD, high definition; NBI, narrow band imaging; WLE, white light endoscopy.
et al have recently confirmed that magnifying NBI observation of mucosa was effective for the assessment of UC follow-up. The endoscopic vascular pattern features were accurately assessed by NBI with magnification and were important predictors of UC relapse.\textsuperscript{31} The iSCAN system has also showed promising results. Neumann \textit{et al} have showed that VCE significantly improves prediction of inflammatory activity and extent with an agreement of 53.85% and 48.71% (p=0.0009) in the HD WLE group and 89.74% and 92.31% in the VCE group (p=0.066).\textsuperscript{32}

We have developed the first VCE (iSCAN) endoscopic scoring system to assess inflammation in UC and have introduced endoscopic findings of mucosal and vascular healing. A new histological scoring system (ECAP system: extent, chronicity, activity, plus additional findings) was also designed to reflect chronic and acute histological changes in UC. In patients with Mayo endoscopic subscore of 0, 30.4% had an abnormal mucosal pattern and 73.9% of them had an abnormal vascular pattern on VCE.

The VCE was able to pick up subtle histological abnormalities underlying the apparently healed mucosa in UC as assessed by the refined ECAP histology scoring system.\textsuperscript{10} The Paddington International Virtual ChromoendoScopy ScOre (PiCaSSO) is a recent VCE scoring system in UC to redefine endoscopic findings of mucosal and vascular healing developed by international experts in optical diagnosis.\textsuperscript{21} The new PiCaSSO embraced all the endoscopic findings of the inflammation in UC and performed better than the previous iSCAN score developed by Iacucci \textit{et al} (table 2). The interobserver agreement of the PiCaSSO score between the experts was very good in the pretest and post-test evaluations and the accuracy of the overall PiCaSSO in assessing histological abnormalities and inflammation by Harpaz score was 57% (95% CI 48% to 65%), by RHI 72% (95% CI 64% to 79%) and by ECAP system 83% (95% CI 76% to 88%)\textsuperscript{21} (with video 1).

The PiCaSSO score also achieves good inter-rater agreement post-training, across all levels of endoscopy experience. Correlation between PiCaSSO and histology was strong, with performance accuracy that is sustainable over time.\textsuperscript{33} Outcomes of mucosal healing defined by PiCaSSO are being assessed in a multicentre study. The MES used MES 0 or 1 as definition of mucosal healing, but it is simply the lower end of the inflammation scoring system. The PiCaSSO can define mucosal healing better with both mucosal and vascular healing and correlates with histological scores better and a training module may improve performance.\textsuperscript{21,33}

Iacucci \textit{et al} have also recently reported the first experience on using the newly introduced iSCAN-OE with magnification (Pentax) to assess subtle inflammatory changes in UC. The new iSCAN-OE endoscopic score correlate very well with histological ECAP (r=0.70; p<0.001). The accuracy of the iSCAN-OE score to detect abnormalities by ECAP was 80% (sensitivity 78%, specificity 100%).\textsuperscript{28} The correlation between iSCAN-OE score and RHI was r=0.61 (p<0.01), and the accuracy to detect abnormalities by RHI was 68% (sensitivity 78%, specificity 50%) (see online supplementary table 1).\textsuperscript{28}

Recently, a novel imaging technique developed by Fujifilm, Japan is LCI. LCI vascular pattern classification was developed to better assess inflammation and MH in UC. The LCI score strongly correlates with histology and interobserver agreement for LCI was excellent between experts and non-experts. VCE and LCI may be a novel approach for evaluating colonic MH and for predicting relapse and outcome in patients with UC and guide monitoring and treatment decision.\textsuperscript{34}

Detailed description of mucosal healing may bridge the gap between endoscopic and histological definitions of mucosal healing. In UC especially histological healing is increasingly being highlighted as reflecting long-term outcome better, but in future more precise endoscopic definitions of mucosal healing may overcome this.

### New paradigm to detect dysplasia in IBD

In a retrospective cohort study in patients with long-standing colonic IBD, HD colonoscopy was associated with a twofold higher dysplasia detection rate on targeted biopsy when compared with SD WLE. Thirty-two dysplastic lesions (27 on targeted biopsy) were detected in 24 patients in the HD group and 11 dysplastic lesions (6 on targeted biopsy) were detected in 8 patients in the SD group.\textsuperscript{22}

In 2003, Kiesslich \textit{et al} performed the first randomised controlled study of 263 patients with long-standing UC (>8 years). The study assessed inflammation extension and detection
of intraepithelial neoplasia (INs) in patients with UC using DCE with target biopsies versus WLE. When using DCE, they demonstrated an agreement between endoscopic prediction of extent of inflammation and histology of 84.5% vs 37% in those having routine WLE (p=0.0001). DCE led to a significant 3.2-fold increase in the number of detected INs in UC as compared with WLE random biopsy sampling. However, this technique is time-consuming, adds costs and while it is standard of care currently, it is likely to be challenged by newer technologies such as VCE in future.

Recently, SCENIC consensus recommended DCE with targeted biopsies as the optimal modality to be adopted in the daily practice to increase the detection colonic dysplasia in patient with IBD. In the SCENIC meta-analysis, eight studies were identified used DCE compared with WLE alone and revealed a significantly greater proportion of patients with dysplasia by using DCE (relative risk (RR)=1.8 (95% CI 1.2 to 2.6) and absolute risk increase of 6% (95% CI 3% to 9%)). Based on a real-life study, random biopsies should still be considered in association with DCE in patients with IBD with a personal history of neoplasia, concomitant PSC or a tubular colon during colonoscopy. In SCENIC consensus unanimous agreement could not be reached on this question, although 80% of the panelists favored targeted biopsies only.

The SCENIC meta-analysis has some limitations and has considered studies using the previous generation of endoscopes with standard WLE rather the new generation of the endoscopes with HD resolution of image. The use of the DCE has been limited mostly to low-quality observational studies and only two randomised controlled trials were conducted. Moreover, the SCENIC consensus did not recommend other endoscopic techniques such as VCE (NBI, iSCAN, BLI) because there were not yet evidence of their effectiveness in detecting dysplastic lesions in patients with IBD compared with DCE.

Recently, a multicentre prospective cohort study from Spain has confirmed the value of DCE in 330 patients with longstanding IBD undergoing surveillance colonoscopy using WLE followed by 0.4% indigo carmine DCE. Results showed a higher dysplasia miss rate with WLE, and 57.4% incremental yield for DCE. Detection rate of dysplasia was comparable between SD and HD colonoscopies (51.5% vs 52.3%, p=0.30). Moreover, dysplasia detection rate was comparable between expert and non-expert (18.5% vs 13.1%, p=0.20) and no significant learning curve was observed (8.2% vs 14.2%, p=0.46).

However, the effectiveness of DCE for IBD surveillance is controversial and debated and there are still many barriers such as learning curve, cost and time as well as procedure reimbursement, are some of the main issues to resolve in order to facilitate and widely implement DCE in routine practice.

Initial studies for dysplasia detection had explored NBI as the first introduced VCE in clinical practice. In a prospective trial from the Netherlands, NBI colonoscopy did not increase the detection rate of dysplastic lesions in patients with long-standing UC. A randomised crossover trial confirmed the same results in patients with UC who underwent both NBI and HD colonoscopy within 3 weeks; of the 11 patients with neoplasia 82% were diagnosed with HD colonoscopy vs 73% by NBI (p=1.0), suggesting that NBI does not significantly improve the detection of neoplasia. Moreover, in the randomised study by Pellisé et al comparing HD colonoscopy plus NBI with HD colonoscopy plus DCE, no significant difference was found in the detection rates of dysplasia between the two groups. In the NBI group, however, there was a higher miss rate of dysplastic lesions as compared with DCE. Furthermore, in three trials which compared WLE and NBI colonoscopies, there was no difference in dysplasia detection rate between the two procedures. Efthymiou et al have shown in a tandem colonoscopy trial that DCE is more sensitive than NBI in detecting lesions for target biopsy but the overall detection of dysplasia was not different between NBI and DCE. Based on these heterogeneous results in these trials, SCENIC consensus have not recommended the use of VCE in the clinical practice.

However, two recent randomised trial have revealed that these electronically enhanced procedures are effective in detecting neoplastic lesions also in patients with IBD.

Iacucci et al have shown iSCAN VCE or HD WLE was not inferior to DCE for detection of colonic neoplastic lesions during surveillance colonoscopy. In fact, in this study HD WLE alone was sufficient for detection of dysplasia, adenocarcinoma or all neoplastic lesions. Bishops et al evaluated whether NBI produced different results than DCE in patients with UC. In this international, multicentre prospective randomised controlled trial, patients requiring surveillance colonoscopy
were randomised to chromoendoscopy or NBI. The dysplasia detection rate was not different between the two groups (21.2% CE vs 21.5% in NBI, p=0.964), but DCE added an average of 7 min to procedure time (table 3).

There are no published data about either the use of BLI or LCI to detect colonic lesion in patients with IBD. Further study in patients with IBD are needed to understand if BLI or LCI may be useful in these patients.

Endoscopic characterisation of colonic lesions in IBD

Accurate endoscopic characterisation of colonic dysplastic lesions is important for therapeutic management. Blackstone was the first to describe the morphological findings of the colonic dysplasia in IBD as a polypoid mass and a plaque-like lesion. SCENIC consensus introduced the modified Paris classification, which included border and ulceration of the lesion and replaced the terms dysplasia-associated lesion or mass (DALM) and adenoma-like and non-adenoma-like in the non-polypoid and polypoid colorectal dysplasia. SCENIC did not consider the endoscopic features and characterisation to predict histology and invasiveness of the lesions detected at surveillance in patients with IBD.

Recently, Sugimoto et al have classified for the first time the morphological features of the high-grade dysplasia (HGD) using the SCENIC consensus. The authors found 84.6% of HGD lesions were non-polypoid in appearance (superficial elevated, flat and depressed) and no HGD lesions with Kudo pit pattern I or II. Superficial elevated lesions were associated with Kudo pit pattern IV–V gyrus-like villous, and flat lesions associated with Kudo pit pattern III–IV large tubular or roundish using magnification endoscopy.

Iacucci et al examined the features of neoplastic lesions associated with IBD, and through multivariate analysis a neoplastic morphology (Is, Ip) OR 2.8 (1.57–5.01, p=0.001), loss in innominate lines OR 1.95 (1.06–3.58, p=0.003) and neoplastic pit pattern (III–V) OR 5.05 (2.58–9.88, p=0.001).

Recently, Bisschops et al assessed the accuracy levels of agreement among experts of Kudo pit pattern in UC with non-magnified colonoscopy and NBI. Using the Kudo pit pattern, experts differentiated between neoplastic and non-neoplastic lesions with a sensitivity of 77%, specificity 68%, negative predictive value (NPV) 88% and positive predictive value (PPV) 46%.

The authors found that expert endoscopists have a moderate-to-substantial interobserver agreement. It is still controversial whether the Kudo pit pattern can be used to predict histology of colonic IBD lesions, especially in the presence of inflammation-associated regenerative pattern and when assessed by using standard colonoscopes without magnification in non-experts hands. Nevertheless, the optimal method of assessing the pit pattern remains still controversial and needs to be explored in future studies. Recently, Iacucci et al have developed, validated and reproduce a new endoscopic classification (Frankfurt Advanced Chromoendoscopic Ibd LEsions) using all imaging modalities for diagnosis of dysplasia in IBD. Flat shape, irregular surface, vascular pattern and sign of inflammation predicted dysplasia (box 1).

Therapeutic management of colonic dysplasia in IBD

The appropriate management of colonic dysplasia in patients with IBD is evolving with advances in endoscopic technology and new devices. SCENIC consensus have also introduced new terminology to describe colonic lesions and the new concept of the endoscopic resectability when dysplasia appears circumscribed. They also recommend continued postpolypectomy endoscopic surveillance as strategy. Despite limited data on endoscopic management of colonic lesions in IBD, endoscopic mucosal resection (EMR) is increasingly adopted to remove
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Confocal laser endomicroscopy

CLE is a relatively new technique which allows ‘in vivo’ microscopic evaluation of the colonic mucosa, like ‘real time histology’ to facilitate diagnosis and decision regarding resectability of lesions.

In the past, CLE could be performed with an endoscope-based equipment (Pentax; iCLE), which is no longer clinically available. In more recent studies, CLE is performed using a through the scope probe (Cellvizio, Mauna Kea; pCLE). During CLE image acquisition, application of fluorescent agents is necessary, either systemic (ie, fluorescein sodium) or topical (eg, acriflavine hydrochloride, cresyl violet acetate) to highlight cellular, subcellular and vessel architecture.50

Many studies with CLE have shown its potential in IBD to differentiate between CD and UC, assess grade of inflammation, predict outcome and characterise colonic dysplastic lesions by targeting biopsies and directing endoscopic management.

Assessment of disease activity

Kiesslich et al first described the role of CLE to assess grade of inflammation in UC. They found that the endoscopic agreement of extent of inflammation with histological findings was 95.0% vs 34.2% in favour of the CLE group (p<0.0001). The agreement with inflammatory activity was 92.5% in CLE group vs 58.9% in WLE group (p=0.046).60 Subsequently, Watanabe et al41 reported inflammatory activity assessment by CLE by grading the crypt, vessels architecture and cellular infiltration. Li et al assessed the inflammatory changes looking at the capillary architecture, the luminal fluorescein leakage and the appearance of the crypts.62 Recently, Tontini et al developed a new endomicroscopy scoring system to differentiate between CD and UC and endomicroscopy prognostic factors to predict outcome of the disease and risk stratification.63 64 Hundorfean et al have validated a new MH endomicroscopy (eMHs) score, which could accurately assess all inflammatory changes. The new eMHs showed high sensitivity, specificity and accuracy values (100%, 93.75% and 94.44%, respectively) correlating well with the histological Gupta score (rs=0.82, p<0.0001).65

Diagnosis of dysplasia

Studies have explored the use of CLE in the detection of dysplasia in patients with IBD. A first randomised CLE study by Kiesslich et al revealed a high diagnostic accuracy to detect dysplastic lesions when using CLE in the setting of UC. They
found that 4.75x more neoplasia were detected in the DCE/CLE group (p=0.005) and the accuracy of CLE at predicting histology was 97.8%, sensitivity 94.7%, and specificity 98.3%.60

Rispo et al further confirmed the accuracy of CLE for the diagnosis of dysplasia in patients with UC. They used a combination of DCE and CLE, and had a dysplasia detection rate of 98%, with CLE having a 100% sensitivity (specificity 90%, PPV 83% and NPV 100%).68 van den Broek et al evaluated the feasibility and accuracy of CLE in UC surveillance. A sensitivity of 65%, specificity 82%, and accuracy of 81% are encouraging, but these were much lower than those patients having HD and NBI (100%, 89% and 92%, respectively).67 The authors explained that hyperplasia and inflammation result in reduced goblet cells and increased striped/irregular epithelium, which may be confused with neoplasia. In addition, neoplasia was associated with regenerative epithelium (crypt types 2a–e) in several cases, contributing to the poor sensitivity. We illustrate pCLE images in figure 5.

Endoscopic molecular labelling to stratify patients for therapy
The concept of tailoring therapy to individual patients based on molecular analysis may play a key role in maximising benefits and minimising risks. The potential future use of molecular imaging to stratify patients with IBD regarding response to targeted monoclonal antibody therapies is exciting but challenging.

Molecular imaging is based on the utilisation of fluorescent probes with specificity towards defined molecular targets and their visualisation by endoscopic devices such as CLE.66 69

The first molecular imaging study has been performed for antitumour necrosis factor (anti-TNF) response.70 The study assessed the number of mTNF-expressing mucosal cells in patients with CD ‘ex vivo’ and ‘in vivo’ after topical application of a GMP fluorescent anti-TNF antibody (fluorescein isothiocyanate (FITC) adalimumab) to the most inflamed area of the mucosa and subsequent imaging by CLE. FITC-labelled monoclonal antibodies cannot be injected intravenously. There was a significant correlation between mucosal mTNF-expression and therapeutic response to subsequent therapy with adalimumab—patients with high amounts of mTNF expressing cells had a significantly higher probability of responding to anti-TNF therapy at week 12 (92%) compared with patients with low amounts of mTNF expressing cells (15%). The sensitivity and specificity for prediction were 92% and 85%, respectively.68 Recently, molecular methods has also been used to determine the response to vedolizumab in patients with UC by evaluating the α4β7 integrin expression69 or to detect dysplasia in patients with UC.70

Molecular endoscopic imaging is an exciting but still a research field and will not be adopted into clinical routine without extensive validation.

Endocytoscopy
Endocytoscopy (EC) is a ‘super’ high-resolution endoscopic technique that enables the real-time observation of cells and nuclei of mucosal surfaces during ongoing endoscopy in vivo with magnification ranging from 450-fold to 1400-fold—it permits prediction of histology and direct sampling virtual biopsy. Recently, a new endocytoscopy system (GIF-Y0002), using only one lens, was introduced; it allows continuous increase of zooming power from the conventional endoscopy level, up to 380-fold. Endocytoscopy requires absorptive staining agents, like methylene blue, toluidine blue or cresyl violet sprayed onto the mucosa and mucolysis with N-acetylcysteine.

Bessho et al developed a score for UC assessment using endocytoscopy termed the Endocytoscopy System Score (ECSS), which included: 1) shape of crypts; 2) distance between neighbouring crypts and 3) visibility of superficial microvessels. For the total score, good agreement between endoscopists was demonstrated k=0.79 (93% CI 0.71 to 0.87, p<0.001). It also showed a strong correlation with histopathological grades for disease activity (r=0.713, p<0.001).71 In a small study of 40 patients with UC, the concordance between endocytoscopy and histology was 100%.72 A further study aimed to identify the usefulness of endocytoscopy to assess MH in patients with UC with MES 0/1, and showed that ECSS correlated well with histology. They also demonstrated features that showed high degree of inflammatory cell infiltrates and therefore could predict relapse.73 Clinical application is limited by the high cost compared with traditional histological techniques. It requires training and determination of learning curve before deciding on potential clinical application (figure 6).

Table 4 illustrates novel endoscopic technologies in evolution.

### Table 4 Novel endoscopic technologies currently in evolution

| Technique | Resolution | Strength | Limitations | Potential application |
|-----------|------------|----------|-------------|----------------------|
| Optical diagnosis | | | Requires specific training to achieve competence | Assessment of inflammation and MH in IBD. |
| ▶ NBI near focus (Olympus) | High with enhanced contrast and digital/filter image enhancement | Detailed definition of vascular and mucosal pattern | | Detection and characterisation of dysplasia in IBD. |
| ▶ ISCAN-OE (Pentax) | | | | |
| ▶ BLI (Fujifilm) | | | | |
| pCLE | Very high | Definition of crypt architecture, vessels and blood flow—near histology-like images | High cost | Assessment of inflammation and MH in IBD. |
| | | | Require injection of fluorescein | Diagnosis of dysplasia in IBD. |
| | | | Dedicated training to achieve competence | |
| Endocytoscopy | Very high | Definition of crypt architectures nuclei and infiltration of cells | High cost | Assessment of inflammation and MH in IBD. |
| | | | Dedicated training to achieve competence | Diagnosis of neoplasia. |
| Molecular imaging with confocal probes | High to very high | Precision medicine stratification and targeted therapies | High cost | Early diagnosis of neoplasia. |
| | | | Research application | Targeted biological therapy in IBD. |
| | | | | |

BLL, blue light imaging; NBI, narrow band imaging; OE, optical enhancement; pCLE, probe confocal laser endomicroscopy.
and higher resolution images thus describing better endoscopic mucosal and vascular features in IBD, as well as lesion characteristic features in dysplasia. It may now enable us to define the intestinal surface in details that may approximate histology. WLE descriptive terms such as loss of vascular pattern and friability may now be replaced with more precise terminology of vascular patterns.

New VCE scoring systems using the new generation of colonoscopes with and without magnification have been developed and endoscopic findings of MH have been described, which correlate well with histological healing. All gastroenterologists should become familiar with the use of electronic chromoendoscopy as these are now integrated in all equipment. Further prospective studies are ongoing to evaluate how these technologies may impact on clinical practice in real life. Randomised studies using VCE or HD images have shown non-inferior detection rate of dysplasia comparing with DCE as standard of practice during surveillance colonoscopy in patients with IBD. If further and larger studies further corroborate these findings, dyeless surveillance colonoscopy may gain a place in clinical practice. In addition, more precise lesion characterisation at surveillance colonoscopy harnessing new refined technologies are permitting local resections in selected lesions rather than pan-proctocolectomy.

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