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DOI:
10.1136/gutjnl-2017-315235

Advanced endoscopic techniques in the assessment of Inflammatory Bowel Disease – new technology, new era

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Funding acknowledgments and Disclaimer:

MI and SG are funded by the NIHR Birmingham Biomedical Research Centre at the University Hospitals Birmingham NHS Foundation Trust and the University of Birmingham. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Abbreviations

SD-WLE=Standard definition white light endoscopy
AFI=Autofluorescence imaging
CD=Crohn's disease
CE=chromoendoscopy
CLE=confocal laser endomicroscopy
GMP=good manufacturing practice
IBD=inflammatory bowel disease
iCE=indigo carmine–aided chromoendoscopy
iCLE=integrated confocal laser endomicroscopy
IN=intraepithelial neoplasia
mCE=methylene blue–aided chromoendoscopy
ME=magnifying endoscopy
NBI=narrow-band imaging
pCLE=probe-based confocal laser endomicroscopy
PSC=primary sclerosing cholangitis
UC=ulcerative colitis
BLI=Blue laser imaging
LCI= Linked colour image
VCE =Virtual electronic endoscopy
SCENIC = international consensus statement on surveillance and management of dysplasia in inflammatory bowel disease

ABSTRACT

Endoscopic assessment of inflammation and mucosal healing is crucial for appropriate management in IBD. Current definition of endoscopic mucosal healing have 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 histologic changes for lesions and inflammation/healing . These technologies can now define subtle inflammatory changes and increase detection and characterisation of colonic lesions in IBD patients.

The best endoscopic technique to detect dysplasia in IBD is still debated. Dye chromoendoscopy with targeted biopsies is considered by SCENIC consensus ~~guidelines~~ the standard of care and recommended for adoption by gastroenterologists in practice. In future it is possible that well trained colonoscopists using HD 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.

***Keywords** : mucosal healing, ulcerative colitis Crohn's disease, intraepithelial neoplasia , , Novel endoscopic techniques, Dye chromoendoscopy ,Optical Enhancement, iScan, electronic virtual chromoendoscopy, Narrow banding image , Blue laser image*

1. 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 inflammatory bowel disease (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 endpoint 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 quiescient 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 Banding Imaging (NBI, Olympus Japan) Optical enhancement iSCAN (iSCAN –OE Pentax , Japan) , Blue Laser Image (BLI , Fujifilm Japan) and Confocal Laser Endomicroscopy (CLE, Mauna Kea France), endocytoscope (Olympus ,Japan) and the emerging endoscopic molecular labeling, modern endoscopy can attain optical characterisation reflecting histology better. In Crohn's disease, 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 (REF). 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~~guidelines~~. 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.(3). 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. (4)

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 (REF Shen Bo)

2.CURRENT STATUS OF ENDOSCOPIC AND HISTOLOGICAL HEALING IN UC AND CD

MH is an important therapeutic endpoint to achieve in IBD and is now widely accepted as a reliable target for optimum management of IBD patients (Selecting therapeutic targets in inflammatory bowel disease). STRIDE) (5). The terms MH and "deep remission"(clinical + endoscopic) are considered new therapeutic targets in the treatment of IBD patients. MH is a term used interchangeably with endoscopic healing though in future these two terms may become more specific. (5)

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. (6-8,18)

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% versus 11.5% p= 0.022) as well as increased risk of steroids or immunosuppressant drugs and hospitalisation (13.0% versus 3.3% p=0.044. Clearly using MES 1 has limitations when considering MH. (6) The time period for observation was at 12 months after total colonoscopy.

The exact histological definition of MH continues to evolve and the most appropriate definition of histological remission has yet to be determined and currently is not considered as a target in UC (STRIDE) (5). 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. (9,10).

(A) Current Endoscopic scoring systems in UC and their limitations

Several scoring systems have been developed using WLE some of which require further validation and noncall ~~have not~~ included the specific endoscopic features and definition of MH. The Mayo endoscopic score (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). (11,12,13,18) Table 1

Travis *et al*. proposed the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) - based on WLE as a reliable and validated score of endoscopic severity in UC as an alternative to the MES. (12). 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 to moderate and severe disease are not clearly described, the disease extension is not evaluated and advantage in the inter-observer agreement over MES has not yet been demonstrated.

The Ulcerative Colitis Colonoscopic Index of Severity (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. (13)

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 (12 13). 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).

(B) 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 endpoint (STRIDE).(5) 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). (14,15) 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 to CDEIS, stronger correlation with the global evaluation of lesion severity (GELS), and is less cumbersome to calculate. (16) However, the exact threshold of SES-CD to define response to therapy as endoscopic endpoint 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 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 (17) Although the score has been adopted in both trials and clinical practice, only a few very recent studies have explored intra- and inter-observer 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 .(17)

3.WHAT ARE THE NEW TECHNOLOGIES THAT ARE AVAILABLE

Recent advances in endoscopic assessment in IBD include dye based Chromoendoscopy (DCE), Virtual Electronic Chromoendoscopy (VCE), Confocal Laser Endomicroscopy (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 to standard WLE. Thus novel endoscopy have started to show promise to approximate histologic readouts. (19)

(A). High Definition & Dye Chromoendoscopy

HD colonoscopy is an advanced technology employing a HD monitor and high resolution charge-coupled device (CCD). HD endoscopes produce image signals with resolution of 850,000 to 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 to 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 IBD patients.(20)

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. (21)

(B).Dyeless Chromoendoscopy

VCE includes optical technologies such as Narrow-Band Imaging (NBI, Olympus), Flexible Imaging Colour Enhancement (FICE, Fujinon) and I-Scan (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 I-Scan methods are based on the reflection of photons to reconstruct virtual images, through a digital post-processing of the endoscopic images, without any filter

application. (22-25)

Two new image-enhanced colonoscopes, using the LASEREO system (Fujifilm, Japan), have recently been developed: blue laser imaging (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 micro-vessels 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.(23)

The new i-**Scan** Optical Enhancement (OE) (Pentax, Japan) is a combination of optical and a digital enhancement chromoendoscopy in a single system. It consists of three different algorithms that can be selected 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. (24)

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. (25) Currently many gastroenterologists are not utilising the full potential of such advanced technologies integrated in current generation of equipment.

44. APPLICATIONS OF NEW TECHNOLOGIES THAT ARE AVAILABLE IN IBD

(A) 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 (8,26,28). 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~~PV~~) in patient with UC(27). They have showed MVP~~MPV~~ 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 standard definition (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% versus 0% p0.0001) and goblet cell deposition (32% versus 5% p0.0006) in the segments with distorted M~~P~~VP. However , NBI has some limitations to assess moderate /severe disease where intra-mucosal 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.(27). Hayashi *et al* have recently confirmed that 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 (28,29) The i-SCAN system has also showed promising results. Neumann *et al* have showed that VCE significantly improves prediction of inflammatory activity and extent with an agreement of 53.85% and 48.71% (p0.0009) in the HD WLE group and 89.74% and 92.31% in the VCE group (p 0.066). (30)

We have developed the first VCE (i-SCAN) endoscopic scoring system to assess inflammation in UC and have introduced endoscopic findings of mucosal and vascular healing. (26) 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 sub-score 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. (8)

The PiCaSSO (Paddington International Virtual ChromoendoScopy ScOre) is a recent VCE scoring system in UC to redefine endoscopic findings of mucosal and vascular healing developed by international experts in optical diagnosis. (19) The new PICaSSO embraced all the endoscopic findings of the inflammation in UC and performed better than the previous i-SCAN score developed by Iacucci *et al.* The interobserver agreement of the PICaSSO score between the experts was very good in the pre-test and post-test evaluations and the accuracy of the overall PICaSSO in assessing histologic abnormalities and inflammation by Harpaz score was 57% (95% CI, 48%-65%), by RHI 72% (95% CI, 64%-79%), and by ECAP system 83% (95% CI, 76%-88%). (19) (video)

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. (31) Outcomes of mucosal healing defined by PICaSSO are being assessed in a multicentre study. The Mayo endoscopic score 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 histologic scores better and a training module may improve performance (31)..

Iacucci *et al* have also recently reported the first experience on using the newly introduced i-scan Optical Enhancement (OE) with magnification (Pentax, Japan) to assess subtle inflammatory changes in UC. The new OE i-scan endoscopic score correlate very well with histological ECAP ($r = 0.70$;$P < 0.001$). The accuracy of the I-SCAN OE score to detect abnormalities by ECAP was 80% (sensitivity 78%, specificity 100 %).(28), the correlation between I-SCAN 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%). (26)

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Recently, a novel imaging technique developed by Fujifilm,Japan is linked colour imaging (LCI). LCI vascular pattern classification was developed to better assess inflammation and MH in UC. The LCI score strongly correlate 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 UC patients and guide monitoring and treatment decision(32)

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

(B) New paradigm to detect dysplasia in IBD

In a retrospective cohort study in long-standing colonic IBD patients, HD colonoscopy was associated with a 2-fold 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 (six on targeted biopsy) were detected in eight patients the SD group. (20)

In 2003 Kiesslich *et al* performed the first randomized 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 vs WLE. When using DCE they demonstrated an agreement between endoscopic prediction of extent of inflammation and histology of 84.5% versus 37% in those having routine WLE (p=0.0001). (33). 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. (34,3)

Recently, SCENIC consensus ~~guidelines~~ 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 8 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 [1.2-2.6] and absolute risk increase of 6% [3%-9%]). (3, 33, 35-37). 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.(Moussata D et al 2018 38). In SCENIC consensus unanimous agreement could not be reached on this question though 80% of the panellists favoured 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 IBD patients compared with DCE.(3)

Recently, a multicentre prospective cohort study from Spain has confirmed the value of DCE in 350 long-standing IBD patients 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% versus 52.3%, p=0.30). Moreover, dysplasia detection rate was comparable between expert and non-expert (18.5% versus 13.1%, p=0.20) and no significant learning curve was observed (8.2% versus 14.2%, p=0.46). (38) 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.

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Initial studies for dysplasia detection had explored NBI as the first introduced VCE in clinical practice. In a prospective trial from Netherlands, NBI colonoscopy did not increase the detection rate of dysplastic lesions in patients with longstanding UC. (39) A randomised cross-over 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 versus 73% by NBI (p=1.0), suggesting that NBI does not significantly improve the detection of neoplasia. (40) Moreover, in the randomised study by Pellise *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 to DCE. (41). Furthermore, in three trials which compared WLE and NBI colonoscopies, there was no difference in dysplasia detection rate between the two procedures. [39-43]. Efthymiou *et al* have shown in a tandem colonoscopy trial that DCE is more sensitive than NBI in detecting lesions for target biopsy but that the overall detection of dysplasia was not different between NBI and DCE [44]. Based on these heterogeneous results in these trials SCENIC consensus ~~guidelines~~ 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.~~

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 showed 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. (45) Bisschops *et al* evaluated whether NBI produced different results than DCE in patients with UC. In this international, multi-centre 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 p0.964), but DCE added an average of 7 minutes to procedure time. (46) (Table 2)
There are no published data about either the use of BLI or LCI to detect colonic lesion in IBD patients. Further study in IBD patients are needed to understand if BLI or LCI may be useful in these patients.

(C) 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 morphologic findings of the colonic dysplasia in IBD as a polypoid mass and a plaque-like lesion (47). SCENIC consensus ~~guidelines~~ 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 (ALM) and non–adenoma-like in the non-polypoid and polypoid colorectal dysplasia (3) SCENIC did not consider the endoscopic features and characterisation to predict histology and invasiveness of the lesions detected at surveillance in IBD patients.

Recently, Sugimoto *et al* have classified for the first time the morphologic features of the High Grade Dysplasia (HGD) using the SCENIC consensus ~~guidelines.~~ 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 IIIL-large tubular or roundish using magnification endoscopy (48,3).

Iacucci *et al* examined the features of neoplastic lesions associated with IBD, and through multivariate analysis a neoplastic pit pattern (III-V) (OR 21.5) and location within the right colon (OR 6.52) were associated with neoplasia (*45).* Also, Carballal *et al* also investigated features of neoplasia and found that lesions in the proximal colon OR 1.86 (1.02-3.40 p0.041), protruding morphology (Is, Ip) OR 2.8 (1.57-5.01 p0.001), loss in innominate lines OR 1.95 (1.06-3.58 p0.003) and neoplastic pit pattern (III-V) OR 5.05 (2.58-9.88 p0.001) (38)

Recently, Bisschops *et al* assessed the accuracy levels of agreement amongst 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%, NPV 88% and PPV 46%. The NPV between DCE and NBI were comparable (p=0.739). The inter-observer agreement was better with DCE (κ 0.332 Vs. 0.224 p=0.001) when using Kudo Pit Patterns. Interobserver a~~A~~greement improved when participants were asked to differentiate neoplastic Vs non-neoplastic where NBI performed better than DCE (κ 0.653 vs. 0.495 p<0.001). Therefore, the authors found that expert endoscopists have a moderate to substantial inter-observer agreement. (49) 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 . (50) Nevertheless ,the optimal method of assessing the pit pattern remains still controversial and needs to be explored in future studies (Figures 1-3)

(D) Therapeutic management of colonic dysplasia in IBD

The appropriate management of colonic dysplasia in IBD patients is evolving with advances in endoscopic technology and new devices. SCENIC consensus ~~guidelines~~ 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 post-polypectomy endoscopic surveillance as strategy.(3) Despite limited data on endoscopic management of colonic lesions in IBD, endoscopic mucosal resection (EMR) is increasingly adopted to remove these lesions. A large retrospective study by Vieth *et al* demonstrated endoscopic resection of polypoid lesions associated with UC is an adequate treatment alternative to proctocolectomy. Following a mean follow up period of 53 months, only 4.6% were found to have further methachronous dysplasia. (-figure 3)However two of the four patients had colitis associated adenocarcinoma treated by surgical resection. When comparing outcomes there was no statistical difference between polypectomy vs. proctocolectomy. This retrospective suggests endoscopic resection is adequate but careful colonoscopy surveillance is vital to exclude further metachronous dysplasia.(51) A meta-analysis by Wanders *et al* on outcomes following endoscopic resection of polypoid lesions in IBD revealed similar results(53). Sessile serrated adenoma may be locally resected at endoscopy by EMR or ESD if it meets SCENIC resectability criteria. However, EMR does have drawbacks and its limitations. The technique for polypoid lesions in general involves removing large lesions, sometimes in piecemeal fashion reducing the chance of accurate histological assessment, and has high recurrence rates than ESD (REF). Endoscopic submucosal dissection (ESD) is ideal endoscopic technique that has been proposed to treat colonic IBD dysplastic lesions which allow endoscopic resection *en bloc*, and is associated with much lower recurrence rates. (52) ESD is still experimental in IBD due the higher complication risks even in experts hands and long term outcomes after lesion removal is not yet clear. (Figure 4)

A pilot study by Iacopini *et al* demonstrated the safety of ESD in nine UC patients, with an excellent curative rate of 70% at 2 years in patients with non-polypoid lesions >20mm. (57) Recently, Suzuki *et al* have confirmed the safety and efficacy of ESD in the IBD population. They reported only 1 recurrence in 32 dysplastic lesions resected by ESD technique at a median of 33 months of follow up, with only 1 patient having delayed bleeding as a complication. However caution should be exercised due to submucosal fibrosis from chronic inflammation which will make the procedure difficult and increase the risk of complications. (53,54)

Recently, Kinoshita *et al* investigated retrospectively 25 patients with UC who underwent colonic ESD for dysplastic lesions . It is recommended ESD technique should be performed in expert hands and post-polypectomy surveillance should be considered. (XXXfigures with ESD) . Therefore, specialised training and adequate clinical experience appear to be necessary to acquire a high level of skill for performing ESD. DCE and VCE may be usefully combined especially to characterise lesions and define margins accurately for EMR and ESD, but this requires further study. In the future we should not be hesitant to implement new

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colon sparing endoscopic management of colonic dysplastic lesions. (55)

5.ENDOSCOPIC TECHNOLOGIES IN EVOLUTION

(A) Confocal laser endomicroscopy (CLE)

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; Tokyo, Japan; iCLE), which is no longer clinically available. In more recent studies CLE is performed using a through the scope probe (Cellvizio, Mauna Kea ; Paris, France; pCLE). During CLE image acquisition, application of fluorescent agents is necessary, either systemic (i.e., fluorescein sodium) or topical (e.g., acriflavine hydrochloride, cresyl violet acetate) to highlight cellular, subcellular, and vessel architecture (56)

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 .

(i) 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% versus 34.2% in favour of the CLE group ($p<0.0001$). The agreement with inflammatory activity was 92.5% in CLE group versus 58.9% in WLE group (p 0.046).(58) Subsequently Watanabe *et al (*57) 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 (58). Recently Tontini *et al* developed a new endomicroscopy scoring system to differentiate between CD and UC (59,60). Tontini *et al* have developed endomicroscopy prognostic factors to predict outcome of the disease and risk stratification . Hundorfean *et al* have validated a new MH endomicrosocpy 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 ($r_s = 0.82$, $P < 0.0001$ (61)

(ii) 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% (56).

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%) (62) 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) (63). (Figure 5)

(iii) 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 IBD patients regarding response to targeted monoclonal antibody therapies is exciting but challenging.

Molecular imaging is based on the utilisation of fluorescent probes with specificity toward defined molecular targets and their visualisation by endoscopic devices such as CLE. (64, 65)

The first molecular imaging study has been performed for anti-tumor necrosis factor (anti- TNF) response (66). The study assessed the number of mTNF-expressing mucosal cells in Crohn's disease patients '*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. (64) Recently , molecular methods has been also been used to determine the response to vedolizumab in IBD patients by evaluating the α4β7 integrin expression (65) or to detect dysplasia in UC patients (66)

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

(B) 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- 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 a*l developed a score for UC assessment using EC termed The Endocystocopy System Score (ECSS), which included: A. shape of crypts; B. distance between neighbouring crypts; and C. visibility of superficial microvessels. For the total score good agreement between endoscopists was demonstrated $k = 0.79$ (95% CI 0.71-0.87 $p<0.001$). It also showed a strong correlation with histopathological grades for disease activity, ($r=0.713$ $p<0.001$) (67). In a small study of 40 patients with IBD the concordance between EC and histology was 100%. (68) A further study aimed to identify the usefulness of endocystoscopy 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 (69). 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)

~~5.ENDOSCOPIC TECHNOLOGIES IN EVOLUTION~~

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6. FUTURE DIRECTION AND CONCLUSIONS

The techniques of defining the mucosa in details at endoscopy are rapidly evolving and dynamic. There are various endoscopic systems that have been developed and introduced in clinical practice and in research and more are in development. The advances in optical technology in endoscopes have resulted in brighter and higher resolution images thus describing better endoscopic mucosal and vascular features in IBD, as well as lesion characterisation 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 colonocopes 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.

Competing Interests

MI: received research support from Pentax, Olympus and Fujifilm; Speaker fees from Pentax

FF: No competing interests

TM: No competing interests

TU: No competing interests

SM: No competing interests

SG: Received speaker fees from Abbvie, Janssen, Takeda

RK: No competing interests

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Figures Legends:

Figure 1: a) High definition b-c)Iscan Optical enhancement (Pentax Japan) with and without magnification showed a low grade dysplastic sessile lesion with Kudo pit pattern IIIL-IV and regular margin

Figure 2: a) DCE b-c) NBI (Olympus Japan) showed a low grade dysplastic sessile lesion with mixed Kudo pit pattern II0 IIIL-IV and regular margin .

Figure 3: a) DCE b-c) LCI(Fujifilm ,Japan) showed a low grade dysplastic sessile lesion with Kudo pit pattern IIIL and regular margin .D) cautery snared polypectomy

Figure 4: a-c) HD and DCE showed flat depressed colonic lesion Paris Iib+IIC d-e) NBI with magnification revealed Kudo pit pattern type IV-V f-i) ESD technique with dual Knife . The lesion was successfully resected en-bloc without perforation Histology reported tubular adenocarcioma T1b(SMI. 300 umm) Negative tumor margins ESD was curative

Figure 5:A-b) VCE –iSCAN (pentax Japan) and DCE with methylene blue 1% showed flat dysplastic lesion Paris classification type IIB with irregular margins c) pCLE showed villiform and irregular crypts with dark epithelium d) Histology with H&E confirmed LGD –DALM

Figure 6: a –b) HD and DCE showed colonic flat elevated dysplastic lesions , Paris IIa+Iib with irregular margins . c) Endocytoscopic image (orig. mag.450) after methylene blue dye stain showed nuclei of epithelial cells are much more strongly stained suggesting cellular dysplasia d) Image (H&E, orig. mag. 400). Confirmed diagnosis of well –differentiated adenocarcinoma Courtesy of Center for Diagnostic and Therapeutic Endoscopy, School of Medicine, Keio University, Japan

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

Endoscopic scores	Endoscopic Technique	Endoscopic Findings	Validation	Pro	Cons

Mayo Endoscopy subscore [[11]] **(1987)**	WLE	Vascular pattern, erythema, friability, erosions and ulceration, bleeding	Partially validated	Easy to use , Widely used in clinical trials	No endoscopic definition of MH Overlap grade 1–2;subjective elements
Ulcerative Colitis Endoscopic Index of Severity (UCEIS)[[12]] **(2012)**	WLE	Vascular pattern (3 levels), bleeding (4 levels), ulceration (4 levels)	Validated	Easy to use; Closely correlated with clinical activity. Validated	No endoscopic definition of MH; No thresholds for mild, moderateand severe disease; No Definition of superficial vs. deep ulcer
Ulcerative Colitis Colonoscopic Index of Severity (UCCIS)[[13]] **(2013)**	WLE	Vascular pattern, granularity, lesions, Friability/bleeding	Partially validated	Easy to use Partially Validated	Requires total colonoscopy;No definition of MH; No thresholds for mild, moderate and severe disease. Developed in a single centre
Modified Mayo Endoscopic score (MMS)[[18]] **(2015)**	WLE	Vascular pattern, granularity, friability, bleeding, ulceration	Not Validated	Easy to use Significant correlation with clinical activity	No established thresholds for mild, moderate and severe disease
Magnifying Colonoscopy UC grade [[27]] **(2006)**	NBI +magnification	Grade 1: pits small, round and regularly arranged Grade 2: pits rather large, oval and somewhat irregular in arrangement Grade 3: pits of various shapes and sizes and irregularly arranged Grade 4: dispersed pits varying in morphology, associated with the presence of small erosioln	Not Validated	Endoscopic Definition of MH	Difficult to be adopted in clinical practice . Required advanced endoscopic technologies and expertise . No threshold of different grade of inflammation
Paddington	VCE-iSCAN	See table 2	Partially	Definition of mucosal and	Requires endoscopy experience No threshold for different levels

International Virtual ChromoendoScopy ScOre (PICaSSO)[19] **(2017)**			Validated	vascular MH; Correlate with histological healing	of inflammation and healing. No clinical outcome
Linked Colour Imaging [32] **(2017)**	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. Required advanced endoscopic technologies and expertise . No mucosal pattern evaluation.

Table 2. The PICaSSO (Paddinghton International Virtual Chromoendosocpy Score) in Ulcerative Colitis

Mucosal architecture	**Vascular architecture**
0) No mucosal defect a) Continuous/regular crypts b) Crypts not visible (scar) c) Discontinuous and or dilated/elongated crypts I) ***Micro-erosions / crypt abscess*** 1) Discrete 2) Patchy 3) Diffuse ***II) Erosions size <5 mm*** 1 – 3) As above	***0) Vessels; no dilatation*** a) Roundish following crypts b) Vessels not visible (scar) c) Sparse (deep) vessels I) ***Vessels; with dilatation*** a) Roundish b) Crowded / tortuous superficial vessels ***II) Intramucosal bleeding*** ***III) Luminal bleeding***

Table 3: Detection rate of dysplasia in studies comparing DCE vs VCE or HD.

DCE vs WLE or HD							
Study	Year	Type of study	Type of endoscopy	N of pts	Dysplasia		
					DCE	WLE	HD
Kiesslich et al[33]	2003	Randomised	DCE vs WLE	165	35	11	
Rutter et al[35]	2004	Non-randomised	DCE vs WLE	100	9	2	
Marion et al[36]	2008	Non-randomised	DCE vs WLE	102	22	16	
Picco et al[37]	2013	Non-randomised	DCE vs WLE	75	22	10	
Carballal et al[38]	2018	Non-randomised	DCE vs WLE vs HD	350	94	27	31
NBI vs WLE or HD							
Study	Year	Type of study	Type of endoscopy	N of pts	Dysplasia		
					NBI	WLE or HD	
Dekker et al[39]	2007	Non-randomised	NBI vs WLE	42	9	13	
Van den Broek et al[40]	2011	Non-randomised	NBI vs HD	48	13	11	
Ignjatovic et al[42]	2012	Randomised	NBI vs WLE	112	5	7	
Leifeld et al[43]	2015		NBI vs HD	159	31	30	
NBI vs DCE							

Study	Year	Type of study	Type of endoscopy	N of pts	Dysplasia	
					NBI	DCE
Pellise' et al[41]	2011	Randomised	~~DCE vs~~ NBI vs DCE	60	10	12
Bisschops et al[46]	2018	Randomised	NBI~~DCE~~ vs DCE~~NBI~~	131	22	31
Efthymiou et al[44]	2013	Non-randomised	NBI~~DCE~~ vs DCE~~NBI~~	44	23	27

iSCAN vs DCE

Study	Year	Type of study	Type of endoscopy	N of pts	Dysplasia		
					iSCAN	DCE	HD
Iacucci et al[45]	2018	Randomised	iSCAN~~HD~~ vs DCE vs HD~~iSCAN~~	270	23	27	42

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