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New endoscopic tools in inflammatory bowel disease

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Abstract

Endoscopic remission is now considered the ultimate long-term goal for treating inflammatory bowel disease (IBD). Recent advances in endoscopic techniques have progressively added new tools to the armamentarium of endoscopists for a deeper assessment and characterisation of the intestinal mucosa. Virtual Electronic chromoendoscopy is widely available in the endoscopic units, leading to a more accurate evaluation of the vascular and mucosal architecture of the colon, reducing the gap with histology, which is considered a favourable long-term measure. In addition, advanced, sophisticated techniques such as endocytoscope and confocal laser endomicroscopy provide insights into individualised and personalised IBD therapy. Finally, high expectations are placed on the advent of Artificial Intelligence (AI) with promising applications that have the potential to revolutionise IBD diagnosis and management. Here, we discuss state-of-the-art of endoscopic techniques and their applicability to accurate assess endoscopic and histological remission, predict response to therapy and detect, characterise and guide treatment of colonic dysplastic lesions. We are seeing the dawn of a new era wherein the applications of these new endoscopic tools, hand in hand with AI, offer the most incredible opportunity to deliver precision medicine to patients with IBD.

KEYWORDS
confocal laser endomicroscopy, endocytoscope, endoscopic remission, inflammatory bowel disease, virtual electronic chromoendoscopy

INTRODUCTION

In the last decade, short- and long-term treatment targets in inflammatory bowel diseases (IBD) evolved, shifting towards objective measures of disease activity.[1,2]

Hence, the role of endoscopy is becoming more and more relevant. In this context, new advanced endoscopic techniques are now available and can provide a more comprehensive endoscopic and histological assessment. Virtual electronic chromoendoscopy (VCE), endocytoscope, and confocal laser endomicroscopy (CLE) converge towards a deeper ultra-structural characterisation of the mucosa, reducing the gap with histology, which is increasingly considered a measure of remission depth and favourable outcome.[2,3]

We provide an overview of the evolution of endoscopic armamentarium to assess the grade of inflammation, healing and detect/characterise dysplasia in IBD with an additional focus on how the implementation of Artificial Intelligence (AI) might revolutionise

clinical management of IBD toward personalised medicine no longer considered hype but reality.

THROUGH THE EYES OF VIRTUAL ELECTRONIC CHROMOENDOSCOPY

VCE is widely available in most endoscopic units and enhances the mucosal and vascular intestinal architecture. Mainly, this helps differentiate between patchy and mild inflammation versus endoscopic remission, a key therapeutic goal in IBD patients. Whilst narrow-band imaging (NBI, Olympus Japan) uses optical filters for a narrow band of blue and green light; optical enhancement iSCAN (iSCAN-OE, Pentax, Japan), flexible imaging colour enhancement and LASEREO system (FICE, Fujinon), which included the linked-colour imaging (LCI), and blue-laser imaging (BLI) use a post-processing digital software algorithm to recreate virtual images.[4] Recently, new software was released from Olympus, the EVIS X1, with two new modes to define better Texture and Colour Enhancement Imaging (TXI) which improves the structure and brightness of the endoscopic images and Red Dichromatic Imaging (RDI) with the purpose to enhance the blood vessels and bleeding.[5]

Currently, the application of VCE in IBD ranges from the assessment of the inflammation to the detection, characterisation and therapeutic management of colonic lesions during surveillance colonoscopies.

- **Endoscopic assessment of endo-histologic remission**

Several new scores have been developed by using VCE platforms. Paddington International Virtual Chromoendoscopy Score (PICaSSO)[6,7] graded mucosal (including elongated crypts, scars, micro erosions, ulcers) and vascular changes (such as sparse vessels, a vessel with dilation or crowded and bleeding) and ranged from 0 to 15 (Figure 1). In a large multicentre international study, endoscopic remission was defined by a value equal to or less than 3, and PICaSSO showed a strong correlation with five histological scores, namely Robarts Histological Index (RHI), Nancy Histological Index (NHI), Villanacci Simple Score, Geboes Score and Extent, Chronicity, Activity and Plus Score (ECAP) with Pearson's correlation between 0.77 and 0.79. Furthermore, it has also shown very good interobserver variability with K agreement of 0.88 and PICaSSO <3 predicted good long-term outcomes at 6 and 12 months with a hazard ratio (HR) of 0.19 and 0.22, respectively.[8] It was initially developed and validated on the i-scan platform, then reproduced on the other endoscopic platforms currently available showing an intraclass correlation coefficient of 0.825. Moreover, the correlation between PICaSSO assessed by NBI and BLI/LCI showed a good correlation with RHI (0.83 and 0.63, respectively) and with NHI (0.79 and 0.65, respectively).[9] Notably, it has been demonstrated that endoscopic remission measured with VCE PICaSSO reflected composite endoscopic-histologic remission, increasingly explored as an ultimate endpoint in Ulcerative Colitis (UC) for predicting specified clinical outcomes at 12 months.[10]

Regarding other platforms, NBI combined with magnification distinguished a three-categories score. BV-H (honeycomb-like blood vessels) and BV-BB (blood vessels shaped like bare branches) were associated with endoscopic healing, whilst BV-V (blood vessels shaped like vines) was linked to histological activity.[11] Moreover, mucosal vascular pattern (MPV) graded by NBI as obscure expressed more acute cell infiltration and depletion of globet cell compared to clear MPV (26% vs. 0% and 32% vs. 5%, respectively).[12]

Similarly, LCI was used to develop three categories of scores such as LCI-A (no redness), LCI-B (redness with visible vessels) and LCI-C (redness without visible vessels), which showed a strong correlation with the histopathology Matts score.[13]

A recent meta-analysis compared the correlations between endoscopy and histologic disease activity scores across several endoscope technologies and found no significant difference among them. However, VCE was more accurate in predicting histological remission than White Light Endoscopy (WLE).[14]

As a more recent VCE, the new Dual Red Imaging (DRI) is a new tool that uses the wavelengths 600 and 630 nm and strongly correlates with Mayo Endoscopic Score (MES). DRI maintained remission at 2 years of follow-up.[15]

To date, PICaSSO is the only validated and reproduced score that all endoscopic platforms can use.

Regarding CD, the current approach for scoring endoscopic activity is the Simple Endoscopic Score (SES-CD),[16] despite several limitations. Therefore, recently, a new scoring tool named the modified multiplier of the SES-CD (MM-SES-CD) has been developed, including the evolution of treatment endpoints into the definition of endoscopic remission.[17] This can predict the achievement of endoscopic remission while on active therapy by considering each parameter's prognostic value. Hence, it is more accurate than the original SES-CD scoring approach for predicting endoscopic remission (comparison of area under the curves on the testing cohort for MM-SES-CD vs. original SES-CD $p = 0.0052$). These implicate that this score can identify patients with a low baseline probability for endoscopic remission with standard therapies in whom treat-to-target monitoring with biomarkers, therapeutic drug concentrations and repeated endoscopy may be most beneficial.

- **Surveillance colonoscopy**

a) for detection of colonic lesions

The most recent European Society of Gastrointestinal Endoscopy guidelines[18] suggested performing surveillance colonoscopy with Dye Chromoendoscopy (DCE) or VCE after appropriate training.

A multicentre study on 188 patients showed no differences between VCE (iscan) and HD-WLE in detecting dysplasia during surveillance colonoscopies (14.9% vs. 24.2%, respectively, $p = 0.14$) with a similar withdrawal time.[19] Similarly, another prospective randomised study conducted on 129 IBD patients showed no difference between DCE and VCE (iscan), with detection of 17.9% versus 11.3%

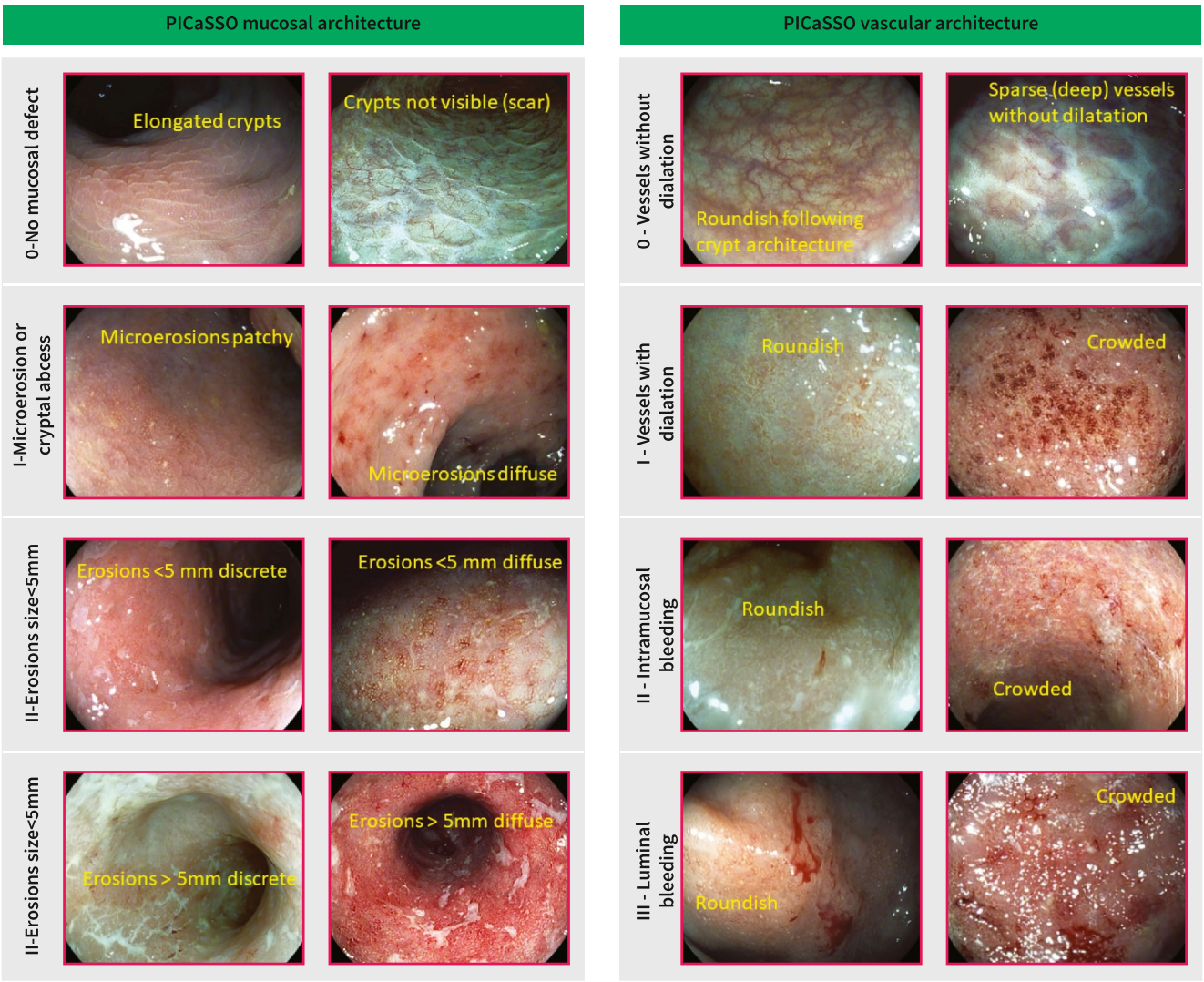

FIGURE 1 Paddington International Virtual Chromoendoscopy Score (PICaSSO) and some examples with iscan

($p = 0.2$). However, in this case, the withdrawal time was significantly higher in the DCE group ($p < 0.001$) compared to the VCE group.[20] A randomised controlled trial (RCT) on 48 patients who underwent both VCE and DCE confirmed these data and included patients' preferences for VCE.[21] More recently, a meta-analysis on 11 RCT (1328 patients) showed no difference between VCE, DCE and HD-WLE in the per-patient analysis; however, in the per-dysplasia analysis, VCE was inferior to HD-WLE (RR 0.62) and not inferior to DCE (RR 0.72).[22] A possible explanation of this can be related to the fact that more lesions can be found once dysplasia is detected in a patient.

However, there is still an ongoing debate about the best technique for surveillance colonoscopy.

Previous studies showed that DCE did not increase dysplasia detection compared with WLE with targeted and random biopsies.[23,24] In recent times, high definition (HD) endoscopy and VCE have become widely available, and hence DCE, WLE, NBI, and VCE with targeted biopsy sampling are all considered acceptable modalities for surveillance when using HD colonoscope.[25]

b) Characterisation of the colonic lesion

Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in Inflammatory Bowel Disease Patients: International Consensus Recommendation consensus has introduced the modified Paris classification, taking into account the morphology (polypoid or non-polypoid), borders and ulcerations to characterise colonic lesions associated with IBD.[26] However, the surface was not considered. However, The Kudo pit pattern, assessed by DCE or VCE, strongly correlated with histology in predicting dysplasia (73% vs. 71% respectively).[27,28]

The Frankfurt Advanced Chromoendoscopic IBD LEsions (FACILE) classification developed with DCE and VCE, considered as the morphology of nonpolypoid lesion (OR 3.13), irregular vessel architecture (OR 3.49), signs of inflammation within the lesion (OR 2.42) and irregular surface pattern (OR 8.89) as predictors of dysplasia.[29]

Recently, European Crohn's and Colitis organization (ECCO) topical review on the endoscopic report introduced the new '5S'

features, which include Site, Size (using biopsy forceps as reference standard), Shape (polypoid, non-polypoid, or lateral spreading tumour, distinct or indistinct borders, presence of ulcers), Surface (Kudo pit pattern or FACILE classification) and Surrounding (mucosal activity, colitis area/non-colitis area, or other lesions in surrounding area).[30]

Moreover, the Japan NBI Expert Team (JNET) classification is based on vessels and surface patterns and ranges from types 1, 2A, 2B to 3, showing prediction of dysplasia and submucosal invasion.[31] It has been used in IBD patients in a small study on 19 UC patients with UC-associated neoplasms, and the JNET type 2A had a low positive predictive value (PPV, 50.0%) and a high negative predictive value (NPV; 94.7%). However, the inter-observer and intra-observer agreements among experts were fair (0.401 and 0.387, respectively).[32]

Furthermore, the Kudo classification assessed by FICE on 205 colonic lesions predicted histology with 91% sensitivity and 76% specificity.[33]

VCE is widely available and can be easily used by pushing '*in real-time*' the button on the handpiece of the scope. The newly VCE validated PICaSSO score can assess inflammation accurately and has made endoscopy closer to histology. In addition, VCE can be adopted as a surveillance colonoscopy technique after adequate training for detection and characterisation of dysplasia associated with IBD, enhancing the morphology, borders, and surface of the lesion and guiding therapy with organ sparing.

CONFOCAL LASER ENDOMICROSCOPY

CLE is a highly innovative endoscopic technique as it provides new insight into several gastrointestinal diseases. It was introduced in 2006 to provide 'in vivo histology' with very high magnification, and resolution of the images of the mucosal layer based on a cellular and subcellular level after applying a systemic fluorescent agent (i.e., fluorescein sodium) injected intravenously before imaging. This system is based on a probe down the accessory channel of an endoscope.

Mauna Kea Technologies, Paris, France (Figure 2). In IBD, CLE was used for structural and functional assessment of the intestinal epithelium, characterisation and classification of inflammatory activity and mucosal healing (MH) in active disease, dysplasia detection and molecular imaging for precision medicine.[3,34,35]

The assessment of MH in IBD was a further application of CLE since it could accurately distinguish between patch/mild inflammation and MH.

Hundorfean[36] developed a MH score by using endomicroscopic scoring system (eMHs). This showed high sensitivity, specificity, and accuracy values (100% with 95% confidence interval [CI] of 15.81%–100%; 93.75% with 95% CI of 69.77%–99.84%, and 94.44%, respectively) and a good correlation with the histological Gupta score (rs = 0.82, $P < 0.0001$) and the endoscopic Mayo subscore (MES) (rs = 0.81%, $P < 0.0001$).

The ability of CLE to predict disease relapse and clinical outcome was first assessed by Kiesslich et al.[37] They observed local epithelial barrier defects with increased cell shedding with fluorescein leakage in IBD patients with subsequent relapse 12 months, indicating that CLE can relapse or define a stable disease when the barrier function is intact.

Karstensen et al.[38] evaluated confocal features in response to various treatment regimens (anti-tumor necrosis factor (TNF), thiopurines, steroids, etc.) in patients with UC using the probe-based CLE system and correlated colonic CLE appearances with histopathology and macroscopic appearance before and after the intensification of the therapy 6–8 weeks later. Fluorescein leakage, microerosions, tortuosity of the crypts, distortion of the crypt openings, inflammatory infiltrates and decreased crypt density were frequently present in active UC as opposed to inactive UC and controls. Interestingly, a decline in histopathology score after medical treatment escalation correlated with diminished crypt tortuosity, distortion of crypt openings, and decreased crypt density.

Buda et al.[39] composed an outcome score by probe confocal laser endomicroscopy (pCLE), combining fluorescence and crypt diameter ($p < 0.01$), able to predict disease flare during a 12-month follow-up period in patients affected by long-standing UC. Pericrypt fluorescence >3100 pixels and a crypt diameter >90 μm increased the probability of disease relapse significantly.

Regarding CD, Tontini et al. demonstrated that CD endomicroscopy findings were predictors of the need for therapy escalation and progression of disease with transmural damage and complication such as strictures or perianal diseases within 1 year of follow-up.[40]

However, in a recent study,[41] pCLE did not add significant advantages in respect of VCE, giving rise to the idea that the new HD-VCE scopes used by well-trained IBD endoscopists are equal to pCLE in assessing the disease. However, future studies are required.

Confocal laser endomicroscopy and molecular imaging

The additional application of molecular endoscopy in IBD allows topical application of labelled probes, mainly antibodies, against specific target structures expressed in the tissue to predict response or failure to biological therapies. This leads to individualised and personalised IBD therapy.

The first molecular target of interest in IBD was TNF. A phase II clinical trial investigated the impact of membrane-bound TNF (mTNF) binding by a fluorescent-labelled adalimumab anti-TNF antibody visualised by CLE 'in vivo' endoscopy on clinical outcome.

Patients with a higher number of cells mTNF positive have a higher probability of clinical relapse compared to patients with lower cells mTNF positive.[42]

Similarly, Rath et al. analysed the ex vivo topical administration of fluorescein-labelled antiadhesion molecule antibody fluorescein isothiocyanate (FITC) labelled α4β7 (vedolizumab) in CD patients.[43]

Patients with positive α4β7–expressing mucosa cells before vedolizumab induction were considered responders to new vedolizumab therapy as opposed to non-responders' patients in whom no positive α4β7–expressing cells were observed during prior ex vivo examination.

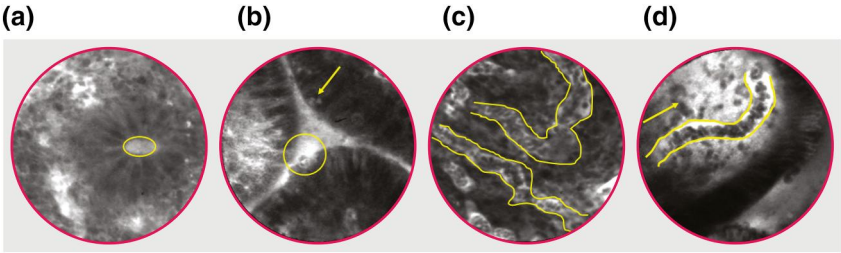

FIGURE 2 pCLE images of (a) crypts architecture; (b) cell sheddings and plumes of fluorescein; (c) tortuosity of the vessels; (d) leakage of fluorescein. pCLE, probe confocal laser endomicroscopy

Preliminary data presented at ECCO 2021 have investigated the predictors of response to biologics in 29 IBD patients using computerised image analysis of pCLE in vivo and the binding of fluorescent-labelled biologics ex vivo. Vessel tortuosity was the only parameter that was significantly altered (reduced) after treatment ($p < 0.05$) in all patients. Additionally, in UC, treatment significantly reduced fluorescein leakage through the colonic mucosa ($p < 0.05$), whereas, in CD patients, it reduced crypt area, eccentricity, and inter-crypt distance ($p < 0.05$).

Targeted biopsies were further taken for FITC-labelled infliximab and anti-integrin-α4β7. The endoscopic procedure was repeated at weeks 12–14 to assess therapeutic response. Ex vivo, higher mucosal binding to the biological agent pre-treatment was associated with a higher likelihood of response to the treatment. Interestingly, the magnitude of this prediction of response was greater in UC (area under the ROC curve (AUROC) 83%, accuracy 77%, PPV 89%, NPV 50%) compared to CD (AUROC 58%, accuracy 64%, PPV 40%, NPV 78%). Noteworthy genes predictive of response were identified. A panel including ACTN1, CXCL6, LAMA4, EMILIN1, CRIP2, CXCL13 and MAPKAPK2 involved in pathways such as inflammation, chemotaxis, TGF-signalling and extracellular matrix showed good prediction of anti-TNF response (AUROC > 0.7).[44]

However, despite the potential advantages, molecular imaging of CLE is far from having widespread clinical use as it requires expert endoscopists, specialised equipment and needs further validation and increases the cost. Nevertheless, it provides the basis for a new era of precisely tailored medicine.

ENDOCYTOSCOPY

Endocytoscopy (ECS; CF- Y-0058-1 prototype, Olympus Japan) is a recent high-ultra magnification endoscopic technique that provides in vivo microscopic imaging during endoscopy, with ultra-high magnification ranging from 450-fold to 1400-fold.

After the application on the mucosa of absorptive agents, such as methylene blue, toluidine blue or cresyl violet, alongside a mucolytic agent (N-acetylcysteine) which allows better penetration of the contrast agent, EC allows looking at cells and nuclei of mucosal surfaces by producing an image close to histology[3] (Figure 3).

Several studies have shown that ECS is a reliable technique to assess endoscopic and histological remission with a high concordance between EC and histology (100%). Of note, EC could differentiate precisely inflammatory cells, such as neutrophilic, basophilic, eosinophilic granulocytes and lymphocytes getting closer to histology.

The significant advantage is the reduced need for biopsy specimens. Indeed, biopsies can assess only a limited area, whereas ECS is an optical diagnosis tool which can sample a wider area in vivo of the colonic mucosa.

Bessho et al.[45] developed the first endocytosocpy score (ECSS), which evaluated the shape and the distance between crypts and the visibility of microvessels. This score showed a strong correlation with Matts's histopathological score and a substantial correlation with Geboes histopathological score.

A further score by Ueda[46] et al. is correlated with MES for mild and moderate UC patients. Deformed pits with distorted crypt lumen with the irregular arrangement or disruptive or disappeared pits were considered active disease features. Therefore, patients with these characteristics had more relapsed in the follow-up period.

Nakazato et al.[44] developed an ECS score (ECSS), which strongly correlated with histological severity. Subsequently, the same authors investigated if ECS can distinguish patients in histological remission from patients with histologically active disease among patients in endoscopic remission.[45] Notable, the ECSS score had good diagnostic accuracy, with a sensitivity of 77% (95% CI, 59–89), specificity of 97% (95% CI, 83–99), and accuracy of 86% (95% CI, 75–93) to predict histological remission in patients with UC.

Recently we assessed the correlation between endocytoscopy and histology in a prospective study including 29 UC patients.[47] An endocytoscopy scoring system (ECSS) was developed based on Nakazato et al. score by including endoscopic findings representative of disease activity (infiltration of the cell). Importantly we found that endocytoscopy features such as crypt architecture, distance between crypts, cellular infiltration, and visibility of microvessels were strongly correlated with RHI ($r = 0.89$; 95% CI, 0.51–0.98) and NHI ($r = 0.86$; 95% CI, 0.42–0.98) but correlated poorly with MES ($r = 0.28$; 95% CI, 0.27–0.70).

Furthermore, RNA sequencing and bioinformatics analysis were performed to define differentially expressed genes/pathways in healing and nonhealing samples and their correlation with endoscopic scores defined by ultra-high magnification with histology scores. We identified genes relevant to TGF-β signalling such as TGFBR2, PDZK1IP1, USP2, and YOD1 and macrophage recruitment into tissues such as RNASET2, neutrophil and plasma cell function

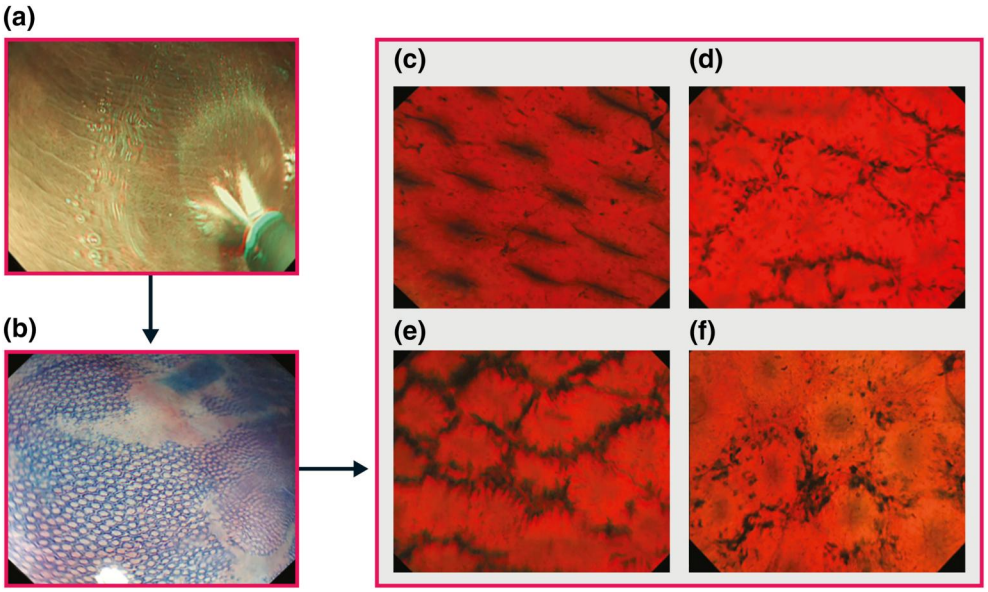

FIGURE 3 After the application on the mucosa of a mucolytic agent N-acetylcysteine, (a) honeycomb-like structure of colonic mucosa with methylene blue 0.2%; endocytoscope images of (b) elongated crypts architecture; (c, d) infilitration of the cells between the crypts; (e) drop out/necrosis of the crypts with infiltration of the cells

RNF4 and PIM2, and tumour suppressor genes human homolog of Drosophila headcase (HECA) and BIN3. These were shared by MES and ECSS-defined healing and histological healing.[48]

In an innovative study by Maeda et al.[49] a computer-aided diagnosis (CAD) based on an endocytoscopy system was used to predict persistent histologic activity and long-term clinical prognoses. CAD revealed good performance measures in terms of sensitivity, specificity, and accuracy of 74% (95% CI: 65%–81%), 97% (95% CI: 95%–99%), and 91% (95% CI: 83%–95%) respectively.

Despite the encouraging results, EC requires dedicated training to achieve good competence before its implementation in clinical practice. However, high costs represent a limitation for its use in routine clinical practice in the management of IBD patients.

ARTIFICIAL INTELLIGENCE IN IBD: HYPE OR REALITY?

The use of AI-assisted endoscopy in IBD is a rapidly evolving area of research with promising results and additional benefits for more precise endoscopic diagnosis.

Given the significant heterogeneity in presentation, disease course, and treatment response in IBD, AI represents a step towards an objective assessment of the disease.

AI's potential applications in IBD include diagnosis, identifying mucosal disease activity assessment, predicting response to therapy/recurrence/complications/hospitalisations, and detecting dysplasia.

The studies on AI-IBD patients published so far are primarily focused on the assessment of inflammation versus remission, mainly using machine learning algorithms based on frames and videos of colonoscopies. To objectively evaluate healing or disease progression, Bossuyt et al. built an algorithm called red density based on an evaluation of the redness map and vascular pattern recognition which correlated with endoscopic and histological disease activity in a cohort of 29 UC patients and control.[50]

A further study by Stidham et al. demonstrated the ability of deep learning techniques to distinguish disease in remission versus moderate/severe disease using MES with AUROC of 0.97 and agreement to human reviewer scores, $\kappa = 0.86$.[51]

Subsequently, Takenaka et al., in a prospective study based on a deep convolutional neural network (CNN) construct on 40,758 images validated in 875 UC patients, developed a system that predicted endoscopic remission with 90% accuracy, $\kappa = 0.80$ and histological remission with 93% accuracy, $\kappa = 0.86$.[52]

Due to high interobserver variability in endoscopy, we expect that AI results could be accurately reproduced, leading to standardising the assessment of disease activity. Furthermore, it can significantly contribute to the accuracy, precision, and reproducibility of central reading in clinical trials. In this context, Gottlieb et al. compare the performance of a recurrent neural network model with a human reader score. Importantly this system produced accurate Mayo and ulcerative colitis endosopic index of severity (UCEIS) scores with agreement/reproducibility of $\kappa = 0.84$ and 0.85, respectively.[53]

Furthermore, we have recently developed the first VCE AI system to accurately distinguish in real-time endoscopic activity and remission in UC colonoscopy videos of both WLE and VCE. A total of 1090 endoscopic videos (638,287 frames) from 283 patients came from the PICaSSO multicenter study were used to develop a CNN to distinguish ER/activity and predict HR/activity. This AI-based CAD system

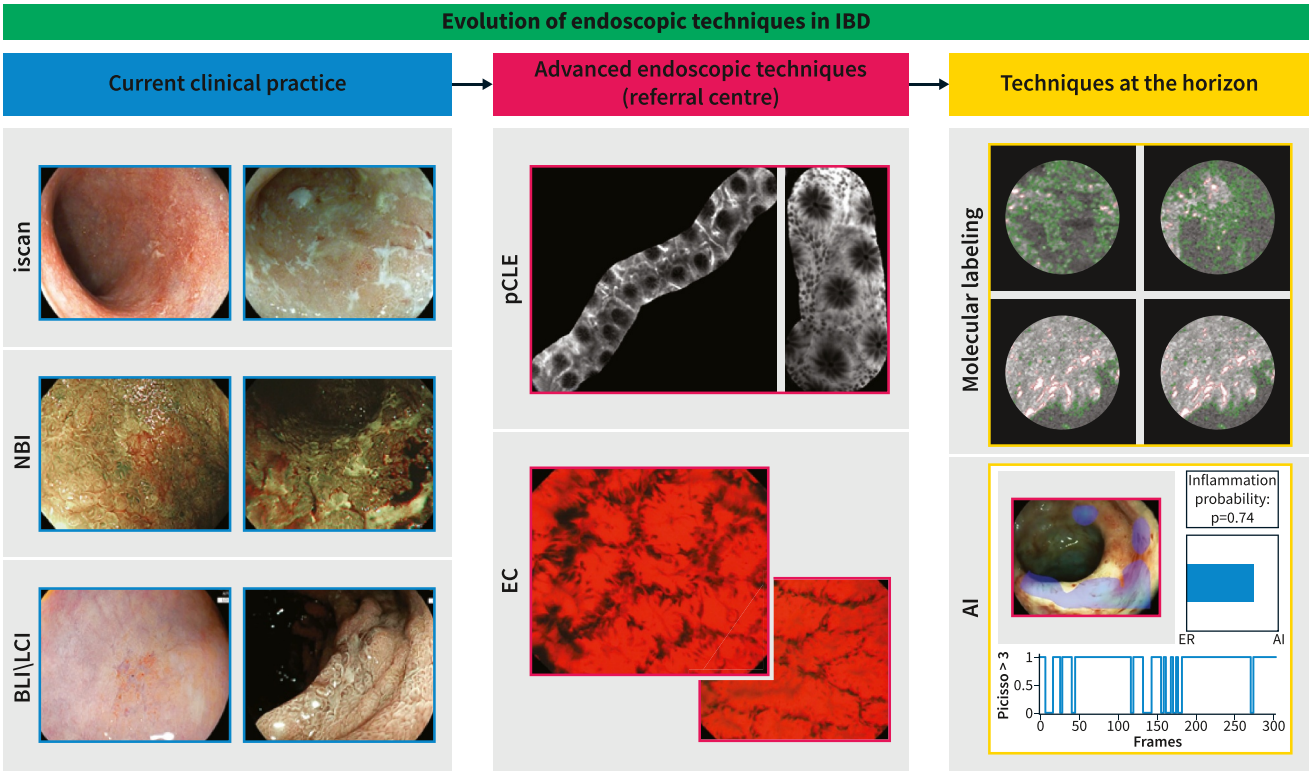

FIGURE 4 Evolution of endoscopic techniques in Inflammatory Bowel Disease (IBD) from the virtual chromoendoscopy in the present, confocal laser endomicroscopy and endocytoscope in some referral centres, to molecular labelling and Artificial Intelligence (AI) in the next future

detected endoscopic remission/activity (PICaSSO ≤ 3) in VCE videos with a sensibility of 79%, specificity of 95%, and the AUROC 0.94. It is worthy to note that it also predicted histologic activity/remission and the occurrence of adverse clinical outcomes.[54]

Finally, a recent study using a set of 614 biopsies from 307 patients with UC enrolled on a prospective multicentre study used a novel deep learning strategy based on a CNN architecture to detect neutrophils, calculate the PICaSSO Histologic Remission Index (PHRI) and identify active from quiescent UC. Importantly this AI algorithm accurately predicted histological remission and differentiated active from quiescent UC with 78% sensitivity, 91.7% specificity and 86% accuracy.[55]

CONCLUSIONS

In recent years several innovative and necessary steps have been taken in the endoscopic assessment of IBD, including prediction of histology, treatment response, and molecular labelling (Figure 4).

Advances in VCE have led to a focus on microscopic details no longer invisible to the human eye, thereby reducing the gap with histology and increasing detection and characterisation of dysplasia associated with IBD. AI systems support clinicians in interpreting and standardising findings such as grading inflammation, detecting adenomatous polyps, predicting histology and thereby clinical outcomes.

However, the road to IBD precision medicine is still challenging.

In the near future bioinformatics tools and integration of multi-omics including faecal metagenomic, serum metabolomic and proteomic profiles will revolutionise IBD management and shed the light on a new fascinating and promising target to achieve: molecular healing and drive precision medicine.

AUTHOR CONTRIBUTIONS

Olga Maria Nardone: designed the work; wrote and draughted the manuscript; approved the version to be published. **Rosanna Cannatelli**: designed the work; wrote and draughted the manuscript; approved the version to be published. **Subrata Ghosh**: concept of the work; revised the article critically for important intellectual content; approved the version to be published. **Marietta Iacucci**: concept of the work; revised the article critically for important intellectual content; approved the version to be published.

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CONFLICT OF INTEREST

No conflict of interest to declare

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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