Beyond white light

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DOI:
10.1055/s-0042-124363

Beyond white light: novel optical enhancement magnification colonoscopy to define mucosal healing in ulcerative colitis patients.

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No financial support was required for this manuscript

Conflicts of Interest

MI: received unrestricted research grant from Pentax USA

None of the other authors have any conflict of interest to declare related with this manuscript

Study design and idea: MI, SG

Data Acquisition: OA, MI, GXS, JH

Analysis of data: OA, MI

Writing of manuscript: MI, SG

Revision of manuscript: MI, RK,RP, SG

This study finding were presented as an oral presentation by Iacucci at the DDW conference at San Diego May 2016 (abstract : Gastroenterology 2016: 39 150(4):S129-S130

Abbreviations:

UC=Ulcerative Colits

OE-iSCAN = Optical enhancement

HD=High definition

EVC= Electronic Virtual chromonendoscopy

RHI= Robarts histological index

SCC= squamous-cell carcinoma

WLE= White light standard endoscopy

ABSTRACT

Introduction: The i-scan Optical Enhancement (OE) with magnification (Pentax) is a recently introduced combination of optical and digital enhancement electronic virtual chromoendoscopy (EVC) which enhances the colonic mucosa in much higher resolution than white light standard endoscopy (WLE). For reference, we also recorded WLE Mayo endoscopic score and biopsies were scored by Robarts Histology Index (RHI) and histological ECAP score.

Methods: Consecutive patients with UC undergoing the new OE-iscan –EPKi 7010 with magnification were enrolled for assessment of the grade of inflammation. The OE-iscan score was divided into mucosal and vascular pattern score as well as overall score. The diagnostic accuracy of OE i-scan was calculated with histology as gold standard (RHI and ECAP).

Results: 50 consecutive patients (41 UC and 9 control) were included in the study (25 men, median age 49y, range 24-79y). The endoscopic appearance by overall OE -iscan

score correlated with ECAP (r=0.70;p<0.0001) and the accuracy of OE-iscan to detect abnormalities by ECAP was 80% (sensitivity 77.7%; specificity 100%). The correlation between Mayo endoscopic score and ECAP score was less strong (r=0.432; p<0.001). Both the OE-iscan vascular and mucosal scores correlated with ECAP score (r=0.65 and 0.71 respectively; p<0.001). The correlation between OE-iscan score and RHI (r=0.61; p<0.01) and the accuracy to detect abnormalities by RHI was 68% (sensitivity 78.1% specificity 50%).
Conclusion : The new OE-iscan may accurately reflect histologic abnormalities demonstrated by ECAP histology score which incorporates the full spectrum of acute and chronic histologic abnormalities.

Keywords: *Optical Enhancement**,** iscan, electronic virtual chromoendoscopy, mucosal healing, ulcerative colitis , ECAP, RHI*

Introduction

Current white light endoscopy (WLE) based colonoscopy scores have limitations in defining mucosal inflammation and healing in ulcerative colitis (UC) when compared with histology which represents the gold standard (1,2). Endoscopic mucosal healing (MH) is becoming established as the main target in the treat to target 'Strategy for Therapies in UC Patients'. (STRIDE) (3) However, the term endoscopic MH is currently empirically defined and a common question asked is 'how deep is deep enough' in MH. A precise endoscopic and histologic assessment of inflammation and its degree are important in clinical practice and in clinical trials (2,9. Stratification of outcomes of IBD and endpoints of therapy maybe further optimized by adoption of advanced endoscopic techniques, which are currently not widely used in routine clinical

practice. Electronic virtual chromoendoscopy (EVC) can provide detailed characterization of inflammatory changes of the intestinal mucosa and better detect subtle residual inflammation when compared with histology. (10-14,16) We recently developed an EVC scoring platform for UC that defines subtle inflammation and MH (14) by specifically characterizing vascular and mucosal pattern changes which correlate very well with the histological scores.

We report our experience on using the newly introduced i-scan Optical Enhancement (OE) with magnification (Pentax, Japan) in assessing inflammatory changes in UC. OE i-scan MagniView™ (Pentax Japan) colonoscopes offer the latest generation of dyeless chromoendoscopy with magnification. (17) This is a unique combination of optical and a digital enhancement chromoendoscopy in a single system which offers the endoscopists better detection and detailed characterization of inflammation and associated neoplastic changes. The system consists of three types of algorithms: OE for blood vessel, glandular ducts and mucosal characterization , Surface Enhancement i-scan 1 (SE) for detection of abnormalities in the gastrointestinal tract and Tone Enhancement i-scan 2 (TE) for pattern characterization. Each of these algorithms can be selected by pressing a pre-assigned button on the hand-piece of the scope (11,17). The newly added OE employs band-limited light to achieve higher overall transmittance by connecting the peaks of the hemoglobin absorption spectrum (415,540 and 570 nm), thus creating a continuous wavelength spectrum. This new system is similar to narrow band imaging(NBI) but with better illumination and brightness by overcoming the spectral distribution and darkness of NBI especially in the areas with a large lumen such as the colon. The optical zoom with magnification further assist in the early detection, characterisation and demarcation by enhancing the images by a minimum of 136 times.

The aims of this study are to assess whether OE-i-scan MagniView ™ (Pentax) has the potential to characterize and define more accurately subtle inflammation and endoscopic MH in UC patients compared with histological inflammation. We also aimed to develop a new redefined virtual OE-iscan Magniview™ mucosal and vascular score that can be more precise to assess changes in UC and reflect histology. We also aimed to compare the

score using the new virtual OE-i-scan MagniView ™ with existing endoscopic and histological scores.

PATIENTS AND METHODS

This was a prospective cohort study performed at a single tertiary referral centre and the Calgary Conjoint Health Services Research Ethics Board of the University of Calgary (CHREB) approved it. Patients with UC referred for surveillance colonoscopy or for assessment of disease activity were enrolled in the study after they provided informed consent. Patients with UC were eligible for the study when they had indication for surveillance colonoscopy, for disease activity assessment or for assessing response to treatment. Patients were excluded when they were pregnant, toxic megacolon or unable to provide informed consent. All patients had OE-iscan colonoscopy with magnification and histology and were assessed by MI, SG and XG respectively.

PATIENTS

Forty-one consecutive patients with inactive or active UC and 9 controls who underwent screening colonoscopy for colonic polyps detection (32 men, median age 49y, range 24-79) during the period from August 2015 to April 2016, were analyzed for assessment of inflammatory activity and MH using the new OE-iscan and MagniView colonoscopy (EPKi 7010, EC-3890LZi, Pentax, Japan). The extent of UC was described according to the Montreal classification (18) Clinical disease activity was determined using the Mayo clinical disease activity score ranging from 0-12 (19). The patient demographics, medication use and CRP concentrations at the time of colonoscopy were also recorded and are shown in table 1.

ASSESSMENT with OE-iscan MagniView ™

After preparation by 4 litres of polyethylene glycol electrolyte lavage solution, patients underwent colonoscopic assessment. Colonoscopies were performed by one IBD

colonoscopist (MI) experienced in novel endoscopic images. The procedures were scheduled as normal colonoscopic practice. The assessment of the OE i-scan with magnification endoscopic images and videos were done by 2 endoscopists (MI, SG) and the inter-observer agreement was calculated *(Kappa agreement statistics)*.

All patients were initially assessed by using Mayo Endoscopic score (0-3) (19) with high definition WL endoscopy (WLE). After that, the three algorithms settings consisted of Surface enhancement i-scan1 for detection of inflammation, tone enhancement i-scan 2 for mucosal and vascular characterization and OE for vessel and detailed assessment of patchy inflammation and MH with and without magnification. (Table3). In the Mayo endoscopic score, mucosal pattern and vascular pattern are not well distinguished from each other. We have previously described that HD i-scan colonoscopy can better characterize vascular patterns clearly and therefore the description of loss of vascular pattern or obliterated in UC by Mayo and UCEIS endoscopic score has been replaced by more detailed description of the abnormalities of vascular pattern such as isolated spiral drop-out vessels by using EVC. We also described and redefined the abnormal mucosal pattern separately under i-scan(15). In the UCEIS system the mucosal pattern was described separately but mainly based on erosions and ulcers. (20).

The new modified OE-iscan virtual chromoendoscopy score was developed based on the our iscan score previously described in our manuscript. (15). The new modified score included all the spectrum of acute and chronic mucosal and vascular changes with more detailed definition of MH . We based our assessment on the framework of our previous i-scan score which recently has been modified for mucosal inflammation that specifically characterizes vascular and mucosal changes which correlate very well with histological scoring systems such as Harpaz and ECAP designed by Gui (15),

The mucosal pattern was graded according to subtle changes of crypt architecture, to micro-erosions to erosions and then ulceration. The vascular pattern changes were graded according to the subtle vascular architecture changes to intra-mucosal bleeding and to frank luminal bleeding. The assessment was done during insertion of the colonoscope.

Mucosal pattern was graded :

1. Normal – Mucosa Healing : roundish/dilated /absent crypts

2. Mild inflammation : roundish crypts with microerosions

3. Moderate inflammation : mosaic –elongated crypts with erosions

4. Severe Inflammation : crypt necrosis with hyperplasia of crypts and ulcers

The vascular pattern was graded :

1. Normal –Vascular Healing: roundish surrounding the crypts /vessels drop-out or isolated spiral vessels

2. Mild Inflammation : roundish /crowded –tortuous vessels

3. **Moderate inflammation :** Dilated vessels with intra-mucosal bleeding

4. **Severe inflammation** : vessels destruction with spontaneous luminal bleeding (Fig1-3)

HISTOLOGIC ASSESSMENT

The mucosal biopsies were taken from the same regions assessed by OE i-scan with magnification. A comprehensive and more detailed histological review which reflected all the chronic and acute changes of inflammation was independently performed by a single gastrointestinal histopathologist (XG) who was blinded to the endoscopic findings. This scoring (ECAP system – **E**xtent, **C**hronicity, **A**ctivity, **P**lus additional findings) system was previous designed independently by XG alongside the i-scan score to assess all even minimal chronic mucosal changes in UC (14). The details of the system are shown in Table 4.

Two other IBD histological grading scheme were used; NYMS (New York Mount Sinai system) developed by Harpaz (21), and the new recently validated Robarts histological index (RHI) were used for comparison (22) with endoscopy. These scores designed for clinical trials but also currently used sometimes in clinical practice, focuses on the activity of colitis, as shown in Table 4

STATISTICAL ANALYSIS

The parametric data are expressed as the mean and SD and categorical data as percentages. Sensitivity Specificity, Accuracy, PPV and NPV of OE-iscan to detect abnormalities by ECAP and RHI were calculated. Correlation between Mayo endoscopic scores , the new redefined OE-i-scan and histological scores used were calculated by the non-parametric Spearman correlation coefficient. The correlation coefficients were used to indicate the linear relationship between different methods but these do not indicate agreement.

The two endoscopist analyzed at least 4 high quality images alongside with a video clip of 60-90 seconds in duration from each patient enrolled and Cohen Kappa statistics were calculated. The images and the videos were anonymous. The inter-observer agreement was calculated .Interpretation of k values was done according to evaluation of Cohen's k with > 0.75 indicating good agreement, 0.4-0.75 fair to good agreement, and <0.4 poor agreement.

Results

Patient details

The extent of UC according to the Montreal classification [16] was as follows: 21/41 (51.2%) patients had left sided UC (E2), 20/41 (48.8%) patients had ulcerative pancolitis (E3). Mayo endoscopic subscore were 0 in 22/41 (53.6%) patients, 1 in 7/41 (17%) patients, 2 in 8/41 (19.5%) patients and 3 in 4/41 (9.7%) patients. (Table 1).

Endoscopic assessment

Relationship between OE-iSCAN and histology in UC

OE-i-scan mucosal pattern grade 1 (normal or MH) was seen in 11/41 (26.8%) patients, grade 2 (mosaic pattern and micro-erosions) was seen in 16//41 (39%) patients, grade 3 (erosions) was seen in 10/41 (24.4%) patients and grade 4 (elongated/necrotic crypts with ulcers) in 4/41(9.7%) patients. OE-iscan vascular pattern grade 1 (roundish, drop-out or isolated vessels) was seen in 8/41(19.5%) patients, grade 2 (roundish/crowded tortuous) was seen in 17/41 (41.4%) patients, grade 3 (intra-mucosal bleeding and dilated vessels) was seen in 12/41 (29.2%) patients and grade 4 (luminal spontaneous bleeding) was seen in 4/41 (9.7%) patients. (Table 2)

The endoscopic appearance by overall OE-iscan score correlated with ECAP (r=0.70; 95%CI: 0.52-0.81; p<0.0001). Both the OE-iscan vascular and mucosal scores correlated with ECAP score (r=0.65; 95%CI: 0.45-0.78; and 0.71; 95%CI:0.54- 0.82 respectively; p<0.001).(Table 5).The accuracy, sensitivity, specificity, PPV, and NPV and of OE-iSCAN to assess inflammation and mucosal healing in UC by ECAP were 80%,78%,100%,100%(95%CI:90-100%),33.3%(95%CI:15.1-58.2%), respectively while the correlation between OE-iSCAN score and RHI was significant (r=0.61; p<0.01). The accuracy, sensitivity, specificity, PPV, NPV of OE-iSCAN to detect abnormalities by RHI were 68% 78%, 50%, 73.5%(95% CI: 56.8-85.3) 56.2%(95%CI: 33.1-76.9), respectively. (Table 5)

The RHI unlike ECAP only scores acute but not chronic histological changes. The NYMS [20] was also used for comparison. This system, which is currently used in clinical practice, focuses mostly on the activity of colitis (Table 4)

Relationship between WL (Mayo endoscopic score) with OE-iSCAN and histology in UC

The overall OE-i-scan scores (mucosal and vascular pattern) were also significantly correlated with Mayo endoscopic score (rs =0.74; 95% CI: 0.58-0.84; p < 0.0001). The

accuracy, sensitivity, specificity, PPV and NPV by Mayo were 62%, 47%, 94%, 94.1%, (95% CI: 73-99), 45.4% (95% CI: 30-62).

The correlation between Mayo endoscopic score and ECAP score was less strong than that between OE i-scan and ECAP scores (r=0.42; 95% CI: (0.17-0.63) p<0.001). The accuracy, sensitivity, specificity, PPV and NPV of Mayo score to assess abnormalities in UC patients by ECAP were 36%, 36% ,NaN, 100 (CI 95%: 82.4-100), 0 (CI 95%: 0-10.7).
The correlation between Mayo endoscopic score and RHI score was also low (r=0.49; 95% CI :(0.24-0.67); p<0.001). The accuracy, sensitivity, specificity, PPV and NPV of Mayo to evaluate inflammation by RHI were 54%, 37.5%, 83.3%, 80 (CI 95: 55-93) 62.8% (CI: 95%: 28-59) (Table 5-6)

Of 41 patients with UC, 23 (54.7%) patients had a Mayo endoscopic subscore of 0. Of those with Mayo endoscopic subscore of 0, 10 of them (23.8%) had an abnormal mucosal pattern and 7 (16.6%) of them had an abnormal vascular pattern on OE i-scan MagniView ^{TM} colonoscopy as shown in Table 2.

The inter-observer agreement of the OE iSCAN scores was calculated and the k statistic was 0.79 (95% CI 0.67- 0.88) and the strength of observation was considered to be ‘good’.

Discussion

We have demonstrated that OE i-scan assessment of mucosal inflammation and healing correlated with histologic scores better that the Mayo endoscopy scores. In addition, OE i-scan detected subtle inflammatory changes by picking up abnormal mucosal or vascular pattern in approximately a quarter of the patients. The Mayo endoscopy score correlated with RHI or ECAP scores less strongly than the OE-iSCAN score; the RHI represents mainly the acute therapy responsive features of histology in UC while the ECAP represents the full spectrum of histology changes, both acute and chronic. This would

support the concept that OE i-scan assessment of the inflammation in UC approximates to histologic changes better than the Mayo endoscopy score, and further demonstrates that EVC, by virtue of assessment of fine mucosal and vascular changes, has the capacity of detecting more of the subtle inflammatory changes as demonstrated by histology. (15)

The clinical implications of assessment of subtle inflammatory changes in UC remain controversial. A recent study has suggested that histologic abnormalities reflect clinical outcomes better than existing endoscopy scores (23). Other retrospective cohort studies have suggested that patients with Mayo subscore 0 have lower colectomy rates than patients with Mayo subscore 1. In patients who were in clinical remission on 5-aminosalicylic acid, doubling the dose of the drug could further reduce fecal calprotectin (24). However, pivotal clinical trials in ulcerative colitis using anti-TNF drugs showed that colectomy rates in patients who achieved Mayo endoscopy score of 0 or 1 at week 8 after commencement of therapy had similar colectomy rates at week 52 (25).

Some of the traditional endoscopic features of UC are based on WLE endoscopy and indeed may date back to endoscopes that provided less details of mucosal and vascular architecture. Loss of vascular pattern, a classic feature of UC, is no longer a feature with EVC assessment, as abnormal vascular pattern rather than complete loss of it is now appreciated. Friability has always been problematic in assessment of the UC affected mucosa as this dates back to the days of rigid sigmoidoscopy. (19) With EVC, abnormal vascular patterns are readily recognized, and intramucosal bleeding can be distinguished from luminal bleeding, reflecting increasing severity of inflammation, and refining identification of ‘friability’. Some of the newer endoscopic scores such as UCEIS and UCCIS have tried to address some of these drawbacks, but these scores also reflect WLE endoscopic appearances, rather than HD resolution with added electronic filter techniques and magnification. These latter scopes are permitting use of a new language around endoscopic abnormalities in UC, including crypt architecture, recognition of micro-erosions, and fine vascular changes around the crypts. (15,26,27)

Histologic changes, both acute and chronic may map to outcomes such as relapses, colectomy as well as risk of dysplasia. There is a clear relationship between the grade and chronicity of inflammation in the colon and the risk of colorectal cancer. Better control of inflammation demonstrated with MH, may be associated with a decreased risk of cancer [27,28, 29]. Therefore endoscopic assessment that reflects the entire spectrum of histologic chronic and acute changes as represented by ECAP may permit future longitudinal prospective studies to determine the clinical meaningfulness of the ability to detect subtle changes. In addition, as the Mayo endoscopy score is a four point score (each point reflecting multiple features), its operational characteristics are limited and may not capture the entire range of inflammatory changes.

The latest OE i-scan MagniView^{TM} is a combination of digital and optical enhancements, the existing i-scan and the new OE, which together can bring additional and more detailed information, especially in the mucosal vascularization pattern to accurately perform almost in vivo diagnosis based on crypt architecture and fine vessel patterns. (17) We have showed accuracy of OE-iscan to be 80 % to assess abnormalities by ECAP, which reflected acute and subtle chronic histological changes in UC (15). Kodashima *et al* have first showed that OE improves endoscopic detection and characterization of esophageal SCC compared with WLE. (30) Robles-Mendranda et al have presented their first experience to assess minimal esophageal inflammatory changes in the GERD patients using the OE system with Magniview. (31) They have showed that the new endoscopic system can predict gastroesophageal reflux disease with high sensitivity and accuracy. Neumann et al have shown that OE-iscan improve polyps characterization .(32) We have also demonstrated that gastroenterologists and physicians without prior experience in novel i-scan OE magnification colonoscopy achieved significant improvement in predicting polyps histology after a brief training session using videos. (33)

This is the first study exploring the use of OE i-scan technology in assessing UC. Our study was aimed at investigating whether subtle inflammation can be detected endoscopically, when Mayo endoscopy score is 0, which is the case with histologic

changes. In pivotal clinical trials both Mayo endoscopy score of 0 or 1 are denoted as mucosal healing, which may be an over-simplication relative to histological changes. Our study has limitations – the scoring system will need to be validated but this will require more familiarity of endoscopists first with the OE-iscan technology before conducting a validation study. Our observations of abnormalities detected by OE i-scan may help in this process of future studies. Our study had single operator, but as availability of the OE i-scan technology widens, multi-operator studies will need to be performed. Furthermore, the good inter-observer variability between two experienced endoscopists in i-scan that have assessed pictures and videos clips gives robustness to the OE-iscan score in addition to the good correlation with the existing and partially validated endoscopic and histological scores.

The responsiveness of our score to therapeutic interventions will require to be determined and short and medium term consequences of persistent subtle inflammation in patients who are in clinical and endoscopic remission by WLE.

In conclusion, advancing endoscopic technology is now promising to give us mucosal details at almost histological levels, capturing both acute and chronic changes and using scopes that can be incorporated in clinical practice.
However, these new endoscopic scores need to be validated and standardized in multicenter international prospective studies.

Legends to figures:

Figure 1: OE-iscan with magnification showed a) the opening dilated crypts of the mucosal healing UC appearance b) a tiny micro erosion with dilated vessels surrounding the opening of the crypts c) microerosions vs erosions d) size of the ulcer

Figure 2: OE-iscan with magnification showed a) crytps necrosis b) dilated vessels surrounding the opening of the crypts c) intramucosal bleeding d) luminal bleeding

Figure 3. OE-iscan with magnification showed a-b) patchy inflammation with dilated vessels surrounding the crypts and alternate areas of MH with by spiral isolated vessels; Histological section (Hematoxylin & Eosin, magnification × 200.) minimally active chronic colitis c-d) MH vascular pattern with spiral isolated vessels; Histological section (Hematoxylin & Eosin, magnification × 200) quiescient chronic UC

REFERENCES

1.Travis SP, Higgins PD, Orchard T, et al. Review article: defining remission in ulcerative colitis. Alimentary pharmacology & therapeutics. 2011;34:113-124.

2.Iacucci M , Ghosh S Mucosal healing –How deep is enough? Dig Dis. 2016;34:160-4

3. Peyrin-Biroulet L, Sandborn W, Sands BE et al. Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): Determining Therapeutic Goals for Treat-to-Target. Am J Gastroenterol. 2015 ;1324-38

4..Korelitz BI. Mucosal healing as an index of colitis activity: back to histological healing for future indices. Inflammatory bowel diseases. 2010;16:1628-1630.

5.Colombel JF, Rutgeerts P, Reinisch W, et al.. Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. Gastroenterology. 2011;141:1194-1201.

6.Sandborn WJ. Mucosal healing with infliximab: results from the active ulcerative colitis trials. Gastroenterology & Hepatology. 2012;8:117-119.

7.Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. The New England Journal of Medicine. 2005;353:2462-2476.

8.Iacucci M, Ghosh S. Looking beyond symptom relief: evolution of mucosal healing in inflammatory bowel disease. Therapeutic Advances in Gastroenterol. 2011;4:129-143.

9.Froslie KF, Jahnsen J, Moum BA, Vatn MH, Group I. Mucosal healing in inflammatory bowel disease: results from a Norwegian population-based cohort. Gastroenterology. 2007;133:412-422.

10.Kiesslich R, Goetz M, Hoffman A, Galle PR. New imaging techniques and opportunities in endoscopy. Nature Reviews Gastroenterol. & Hepatol. 2011;8:547-553.

11.Kodashima S, Fujishiro M. Novel image-enhanced endoscopy with i-scan technology. WJG. 2010;16:1043-1049.

12.Atkinson M, Chak A. I-Scan: chromoendoscopy without the hassle? Dig and liver dis 2010;42:18-19.

13.Kudo T, Matsumoto T, Esaki M, Yao T, Iida M. Mucosal vascular pattern in ulcerative colitis: observations using narrow band imaging colonoscopy with special reference to histologic inflammation. International Journal of Colorectal Disease. 2009;24:495-501.

14.Esaki M, Kubokura N, Kudo T, Matsumoto T. Endoscopic findings under narrow band imaging colonoscopy in ulcerative colitis. Digestive Endoscopy : . 2011;23 Suppl 1:140-142.

15. M Iacucci, M Fort Gasia, C Hassan, Ret al . Complete mucosal healing defined by endoscopic Mayo subscore still demonstrates abnormalities by novel i-SCAN endoscopic and refined histological gradings. Endoscopy 2015;47:726-734.

16. Seiko Hayashi, Shin-ei Kudo, Noriyuki Ogata et al Narrow-Band Imaging Efficiency for Evaluation of Mucosal Healing/ Relapse of Ulcerative colitis.
GIE Vol 83 ,Issue 5 , 154

17.Helmut Neumann, Mitsuhiro Fujishiro, C. Mel Wilcox et al Present and future perspectives of virtual chromoendoscopy with i-scan and optical enhancement technology *Digestive Endoscopy* 2014; **26**: 43–51

18.Silverberg MS, Satsangi J, Ahmad T et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel dis- ease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. Can J Gastroenterol 2005; 19: 5 – 36

19.Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. The New England Journal of Medicine. 1987;317:1625-1629.

20.Travis SP, Schnell D ,Krzeski P et al.Reliability and initial validation of the ulcerative colitis endoscopic index of severity.Gastroenterology. 2013 ;145:987-995

21.Hefti MM, Chessin DB, Harpaz NH, Steinhagen RM, Ullman TA. Severity of inflammation as a predictor of colectomy in patients with chronic ulcerative colitis. Diseases of the Colon and Rectum. 2009;52:193-197.

22.Mahmoud H Mosli, Brian G Feagan, Guangyong Zou, et al Development and validation of a histological index for UC Gut 2015;0:1–9.

23.Bryant RV, Burger DC1, Delo J, Walsh AJ et al Beyond endoscopic mucosal healing in UC: histological remission better predicts corticosteroid use and hospitalization over 6 years of follow-up. Gut. 2016;65:408-14.

24.Osterman MT,Aberra FN,Cross R,Liakos S, et al
Mesalamine dose escalation reduces fecal calprotectin in patients with quiescent ulcerative colitis.Clin Gastroenterol Hepatol. 2014 ;12:1887-93

25.Colombel JF, Rutgeerts P, Reinisch W et al
Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. Gastroenterology. 2011 ;141:1194-201

26.Allez M, Lemann M. Role of endoscopy in predicting the disease course in inflammatory bowel disease. WJG. 2010;16:2626-2632.

27..Gomes P, du Boulay C, Smith CL, Holdstock G. Relationship between disease activity indices and colonoscopic findings in patients with colonic inflammatory bowel disease. Gut. 1986;27:92-95.

28. Choi CH1, Ignjatovic-Wilson A, Askari A,et al Low-grade dysplasia in ulcerative colitis: risk factors for developing high-grade dysplasia or colorectal canc**er.** Am J Gastroenterol. 2015 ;110:1461-71

29.Rutter M, Saunders B, Wilkinson K, et al. Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis. Gastroenterology. 2004;126:451-459.

35.Ullman TA, Itzkowitz SH. Intestinal inflammation and cancer. Gastroenterology. 2011;140:1807-1816.

30. Kodashima S,Fujishiro M, Ono S et al Evaluation of an new image-enhanced endoscopic technology using band limited light for detection of esophageal squamos cell carcinoma Dig Endosc. 2014 Mar;26(2):164-71

31. .Carlos Robles-Medranda, Manuel Valero, Miguel Soria ALcívar, et al Minimal Esophageal Lesions Detected By Digital Chromoendoscopy Using Optical Enhancement System™ Associated to High Definition With Optical Magnification in Non Erosive Reflux Disease (NERD) GIE Vol.83 , Issue 5 , 151-152

32.Helmut Neumann, Heinz Albrecht, Silke Löffler et al Development and Validation of a Simple Classification System for In Vivo Diagnosis of Colorectal Polyps Using the Newly Introduced Optical Enhancement (OE) Technology GIE Vol.83,Issue 5, 402

33.Marietta Iacucci , Fort Gasia Miriam, Oluseyi Akinola et al
Accuracy and Inter-Observer Agreement for Characterization of Colonic Polyps Using the New Optical Enhancement -iSCAN Closefocus™ Colonoscope Gastroenterology 2016,: 39 150(4):S769

Tables

Table 1. Baseline characteristics of Enrolled Cohort
(n= 41 UC and 9 controls)

Clinical data	Patients
Age, median (range) years	49 (24-79)
Male n (%)	32 (64)
Disease duration (mean± SD range, years)	17.1 ± 11.7 (1-47)
Extension n (%)	
Proctitis	0 (0)
Pancolitis	21 (51.2)
Left-sided	20 (48.8)
Mayo endoscopic score n (%)	
0	22 (53.7)
1	7 (17.1)
2	8 (19.5)
3	4 (9.8)
Current medication n (%)	
None	2 (4.9)
Mesalamine	21 (51.2)
Azathioprine/Methotrexate	3 (7.3)
Anti-TNF	5 (12.2)
Combination treatment	10 (24.4)
Steroids	0 (0)
Laboratory Markers mean ± SD	
CRP, mg/L	5.3 ± 11.3

Mayo Endoscopic subscore	0E-iSCAN mucosal pattern				OE-iSCAN vascular pattern			
	1	**2**	**3**	**4**	**1**	**2**	**3**	**4**
0	10	13	1	-	7	16	1	-
1	1	-	5	-	1	-	5	-
2	-	6	-	-	-	1	5	-
3	-	-	1	4	-	-	2	3

Table 2 Assigned scores: Mayo Endoscopic score (WLE) and OE-iscan mucosal and vascular pattern

Table 3. The OE-iscan modes settings used in this study to assess and characterize inflammation and mucosal healing in UC

OE-i-scan	i-scan 1 Surface enhancement	i-scan2 Tone enhancement	i-scan 3 Optical enhancement
Brightness	0	+2	+2
Average -Peak	Ave	Ave	Ave
Blue	0	0	0
Red	0	0	0
Enhancement	Low/+2	Low/+2	Low/+2
Surface Enh.	+5	+5	NA
Tone Enh.	Off	C	NA

OE	Off	Off	Mode1
Inflammation/Healing	**Detection**	**Pattern Characterization**	**Vessel Characterization**

Tables 4 Histological scores

Table 4a. IBD Histological Grading Proposal (ECAP System)

Histopatology	Grade/score
Extent of inflammation (E)	
Focal	1
Multifocal (patchy)	2
Diffuse	3
Chronicity (C)	
C1.Crypt Architectural Alteration	
None	0
Focal Alteration	1
Patchy Distortion (<50%)	2
Diffuse Distortion (>50%)	3
C2.Paneth cell Metaplasia	
None	0
Present	1
Activity of inflammation (A)	
A1.Surface epithelium	
Normal	0
Reactive changes (mucin depletion/villiform)	1
Neutrophilic infiltration	2
Erosion	3
Ulceration	4
A2.Neutrophilic cryptitis	
None	0
>5%	1
<50%	2
>50%	3
A3.Crypts Abscess	4
None	0
Present	1
A4.Crypts Destruction	
None	0

Crypt Destruction	1
A5.Lamina Propria Mononuclear Cellularity	
Normal	0
Mild increase	1
Moderate increase	2
Severe increase	3
A6.Basal Plasmcytosis	
None	0
Focal	1
Diffuse	2
A7.Lamina Propria Neutrophilic Infiltration	
None	0
Rare	1
Scattered	2
Extensive	3
Plus/Others(P)	
P1.Lamina Propria Eosinophilic Infiltration	
None	0
Mild	1
Moderate	2
Severe	3
P2.Lymphoid Follicle /Aggregates	
None	0
Rare	1
Prominent	2
Total Score	

Table 4b. Robarts Histologic index score

Component
Chronic inflammatory infiltrate
0=No increase
1=Mild but unequivocal increase
2=Moderate increase
3=Marked increase
Lamina Propria neutrophilis
0=No increase
1=Mild but unequivocal increase
2=Moderate increase
3=Marked increase
Neutrophils in epithelium
0=None
1=<5% crypts involved
2=<50% crypts involved

3=>50% crypts involved
Erosion or ulcerations 0=No erosions ,ulcerations or granulation tissue
1=Recovering epithelium+adjacent inflamamtion
1=probable erosion-focally stripped
2=unequivocal erosion
3=ulcer or granulation tissue

Table 4c. New York Mount Sinai scoring system

Score	Description
0 – inactive colitis	No cryptitis
1 – mildly active colitis	Cryptitis in <50% of crypts
2- moderately active colitis	Cryptitis in >50% of crypts
3 – severely active colitis	Ulceration or erosion

Table 5. Spearman's rank correlation coefficient between Mayo and OE-iscan scores and Histology

Endoscopic scores	Harpaz	ECAP	RHI	P value
Mayo 95%CI	0.55 (0.32-0.71)	0.42 (0.17-0.634)	0.49 (0.24-0.67)	P<0.001

OE-iscan Mucosal 95%CI	0.61 (0.41-0.26)	0.71 (0.54-0.82)	0.61 (0.4-0.75)	P<0.001
OE- iscan Vascular 95%CI	0.62 (0.41-0.76)	0.65 (0.45-0.780	0.56 (0.33-0.72)	P<0.001
OE-iscan Overall 95%CI	0.64 (0.44-0.77)	0.70 (0.52-0.81)	0.61 (0.-4-0.75)	P<0.001

Table 6. Sensitivity, Specificity,Accuracy, PPV and NPV of OE-iscan

	OE-iSCAN & WL Mayo	OE-iSCAN &ECAP	OE-iSCAN &RHI	WL-Mayo &ECAP	WL-Mayo &RHI
Sensitivity ,(%) 95%CI	**47 (0.31-0.63)**	**78 (0.63-0.84)**	**78.1 (0.61-0.89)**	**36 (0.24-0.49)**	**37.5 (0.22-0.54)**
Specificity,(%) 95%CI	**93.7 (0.71-0.98)**	**100 (0.56-100)**	**50 (0.29-0.70)**	**NaN -**	**83.3 (0.60-0.94)**
Accuracy,(%)	**62**	**80**	**68**	**36**	**54**
PPV, (%) 95%CI	**94.1 (73-98.9)**	**100 (90-100)**	**73.5 (56.8-85.3)**	**100 (82.4-100)**	**80 (55-93)**

NPV,(%)	**45.4**	**33**	**56.2**	**0**	**42,8**
95%CI	**(29.8-62)**	**(15.1-58.2)**	**(33.1-76.9)**	**(0-10.7)**	**(28-59)**