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Advanced Endoscopic Imaging Techniques for the Study of Colonic Mucosa in Patients with Inflammatory Bowel Disease

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Background. Crohn's disease and ulcerative colitis are inflammatory bowel diseases (IBD) associated with colorectal cancer risk in long-standing diseases. In order to assess the colonic mucosa and to discover dysplastic or neoplastic lesions, advanced endoscopic techniques are needed. Such techniques are detailed in this review: chromoendoscopy, autofluorescence imaging (AFI), narrow band imaging (NBI), i-SCAN, Fujinon Intelligent Color Enhancement (FICE) and confocal laser endomicroscopy (CLE).

Aim. The aim of the review is to describe and establish the clinical impact of advanced endoscopic techniques, that could be used in IBD patients'examination in order to assess mucosal healing, microscopic inflammation, dysplasia or neoplasia.

Materials and Methods. A literature research about new endoscopic approaches of patients with IBD was made.

Results. A lot of studies have been performed to reveal which imaging technique might be used for IBD surveillance. Regarding dysplasia or neoplasia detection and mucosal healing or inflammation assessment, CE proved to be superior to white light endoscopy (WLE), while NBI and AFI did not show an encouraging result. I-SCAN did not improve the colonoscopy quality while FICE has been used in a few studies. CLE could be used to characterize a lesion, providing the same results as conventional histology.

Conclusion. At the moment, CE is the only technique which has been included in guidelines for IBD surveillance. CLE can be used to assess any lesion detected with WLE during surveillance, while the other imaging techniques require more studies to determine their efficacy or inefficacy.

Key words: autofluorescence imaging, narrow band imaging, i-SCAN, confocal laser microscopy, inflammatory bowel disease.

INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) represent the two major types of inflammatory bowel disease (IBD). They evolve with remission and relapse periods. UC affects the rectum with diffuse inflammation that can extend to the entire colon (causing pancolitis). The inflammation in CD may be transmural, with "skip lesions" that can affect any part of the gut from the mouth to the anus [1].

Usually, IBD can be differentiated by clinical, radiologic or endoscopic and histologic criteria. Sometimes, patients may present only with colonic manifestations and the distinction between CD and UC can be difficult. For an accurate diagnosis, some emerging endoscopic techniques can provide additional information over conventional white light endoscopy (WLE). They can be used in IBD patients' surveillance in order to assess microscopic inflammation, dysplasia or neoplasia [2].

AIM

The aim of the review is to describe and establish the clinical impact of advanced endoscopic techniques that could be used for the study of colonic mucosa in IBD patients, in order to assess mucosal healing or inflammation, dysplasia or neoplasia

We describe the following endoscopic techniques: magnification chromoendoscopy, autofluorescence imaging, narrow band imaging, i-SCAN, Fujinon Intelligent Color Enhancement and confocal laser endomicroscopy.

MATERIALS AND METHODS

A literature electronic research about new endoscopic approaches of patients with IBD was performed on PubMed, MEDLINE, Researchgate, ScienceDirect, using the following keywords: chromoendoscopy, autofluorescence imaging, narrow band imaging, FICE, i-SCAN, confocal laser endomicroscopy, new imaging techniques and approaches in IBD. We have included articles starting from 2003 till present, full access articles and conclusive results from abstracts.

MAGNIFICATION CHROMOENDOSCOPY

Chromoendoscopy (CE) uses different dye agents sprayed on the mucosal surface, allowing

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the visualization of specific areas (i.e. the vascular network) or to distinguish among different types of epithelium that are not easily recognized with WLE. CE can visualize minute changes that might occur in the surface pattern of the GI tract [3]. CE associated to high-resolution magnifying endoscopes provides a better mucosal surface analysis [4]. Three types of dye agents can be used: (I) absorptive agents (Lugol, methylene blue, cresyl violet and toluidine blue), (II) contrast agents (acetic acid, indigo carmine) and (III) reactive staining agents (Congo red, phenol red), being applied via standard spraying or biliary ERCP catheters [4–6]. These dyes react differently with the mucosa: absorptive stains are absorbed by specific epithelial cells, contrast stains penetrate mucosal crevices improving the surface visualization and mucosal irregularities, while reactive stains produce a chemical reaction with specific cellular constituents, resulting in a colour change. The dyes may be sprayed on a small area (targeted CE) or on the whole colon (pan-colonic CE) using a spray catheter introduced down the endoscope working channel [7, 8]. In pan-colonic CE, the endoscope and catheter are directed toward the colonic mucosa and spiral movements are made while withdrawing the endoscope tip and spraying the dye [9]. Once a segment has been sprayed, the excess dye is aspirated and the endoscope is reinserted in the proximal segment to examine it; when this is done the next segment is sprayed and so on till the entire colon is examined [10].

The abnormal mucosa may stain positively (i.e. taking up the dye) or negatively (i.e. remaining unstained or understained) [8] (Figure 1). Cells may react differently to the stains: dysplastic cells have a decreased uptake of these dyes compared to normal cells [11]. In cases with low inflammatory activity, the cryptal opening has a regular staining pattern; a reticulated intercalation of crypts with little or no uptake of the dyeing agent is seen in highly inflamed areas (for example in UC) [12].

Combining magnification with CE allows a detailed mucosa surface analysis of suspected lesions by using the pit pattern classification with five types and different subtypes (Table 1).

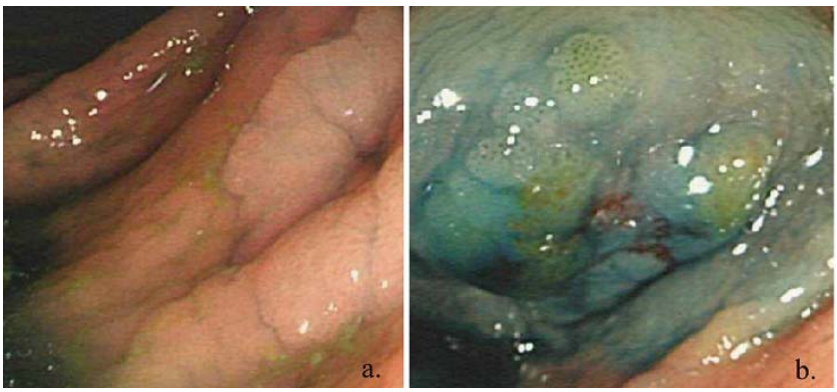

Figure 1. Dysplastic lesion in a patient with UC. Images obtained during WLE (a) and methylene blue CE (b).

Table 1
Modified Kudo Criteria for Pit Pattern Classification [13]

Pit Type	Description	Morphologic Appearance
I	Round and regular pits (normal aspect)	
II	Stella/onion-shaped pits (hyperplastic)	
III_S	Round or compact pits, but smaller than type I	
III_L	Tubular or large pits	
IV	Elongated or sulcus or large pits	
V	Irregular and nonstructural pits, having all sizes	

Type I and II are non-neoplastic lesions, but types III to V indicate neoplastic lesions [13]. To enlarge the image, magnifying endoscopes "zoom in" by using a movable lens which improves imaging of fine mucosal structures and the microvascular network. A transparent cap is fixed at the tip of the endoscope for maintaining a distance of 2-3 mm between mucosa and the endoscope, to obtain a focused image [4].

CE is being increasingly used in IBD surveillance because it allows targeted biopsies, although it has its limitation, as the length of procedure or the fact that the contrast agents do not always cover the entire investigated area [14]. CE is a safe procedure, as long as the stains are used with proper concentrations [6].

AUTOFLUORESCENCE IMAGING

Autofluorescence imaging (AFI) is based on fluorescent light emitted by certain endogenous substances from the tissues (i.e. fluorophores) such as collagen, nicotinamide adenine dinucleotide (NAD), flavinor porphyrins, when they are excited with ultraviolet light (<400 nm) or short wavelength light (mostly blue). Autofluorescence is influenced by changes in tissue architecture, the biochemical environment, metabolic status and light absorption properties (determined by haemoglobin concentration) – which occur mainly in neoplasia, inflammation and also ischaemia [15-17]. If mucosa or the epithelial layer are thickened autofluorescence is also influenced [18]. Normally, the tissue is pseudocoloured as green, blood vessels as dark green and neoplasia appears as magenta. A suspect lesion (AFI-positive lesion) is an area which has a different colour than the surrounding mucosa and a defined circumferential margin [15]. AFI uses only natural tissue fluorescence, so no drug administration or dye spraying are needed [19].

In neoplastic tissues autofluorescence becomes abnormal due to several cellular changes in the superficial layers:

- increased nuclear-cytoplasmic ratio (nuclei show no autofluorescence if compared with the cytoplasm, so the autofluorescent signal detected will decrease in that mucosal area)
- metabolic change of NADH to its oxidized form NAD+ (a non-fluorescent molecule)
- blue-green collagen and elastin autofluorescence is less intense in thickened mucosa
- neovascularization, which induces increased haemoglobin concentration that will absorb the autofluorescence light [15-20].

New endoscopes combine the latest generation of autofluorescence technology as part of a videoendoscope with high-resolution WLE and NBI. (EVIS LUCERA SPECTRUM; Olympus Medical Systems Co, Tokyo, Japan). On the tip of the endoscope there are two monochromatic charge-coupled devices (CCDs) for image capture, one for WLE and NBI and one for AFI. The AFI mode involves a filter in front of a xenon light which generates blue and green light. In front of the AFI CCD there is another filter that blocks the blue light excitation and enables reflected green light and tissue autofluorescence (500-630 nm) to pass through. A video processor integrates the sequentially captured images of green reflectance and autofluorescence into a real-time pseudocolor image, where normal mucosa is green and dysplastic lesions dark purple. AFI is considered a safe procedure for the examination of IBD patients, because it does not use any contrast agents [21] (Figure 2).

NARROW BAND IMAGING

Narrow band imaging (NBI) is an optical image enhancement technology that uses a special set of filters interposed after the light source, to restrict white-light spectrum to two narrow bands of different wavelengths (blue at 415 nm and green at 540 nm) [22].

The optical filter divides the white light in 415 and 540 nm wavelengths light. The obtained light illuminates the mucosa which reflects back another light that is captured by a CCD mounted at the distal portion of the videoendoscope. This device converts the captured light into digital values which will reconstruct the image in a specific videoprocessor [23, 24].

The principle of NBI is the longer the wavelength of light, the deeper the penetration into tissues. The vessels from the superficial capillary network absorb the 415 nm channel; they appear brown, enabling the analysis of the mucosa's superficial architecture (mucosal pattern). The 540 nm wavelength light penetrates deeper and highlights the vessels in the depth of the mucosa/submucosa, which appear cyan [23, 25]. In WLE, fine mucosal blood vessels and thick submucosal blood vessels appear as red areas [26]. By analysing vessel architecture, mucosa can be classified as normal or abnormal (Figure 2): in tumours the vascularization

is more pronounced and irregular; in gastrointestinal bleeding, the absorption of blue and green light are increased and, therefore, the image resulted is darker [24]. By combining NBI with magnifying endoscopy (up to × 150, but usually × 80 is used) and high-definition, more precise images can be achieved [23]. For maintaining an adequate and focused distance, a transparent hood is fixed at the tip of the endoscope [22], to enable better visualization of dysplasia or malignancy [27].

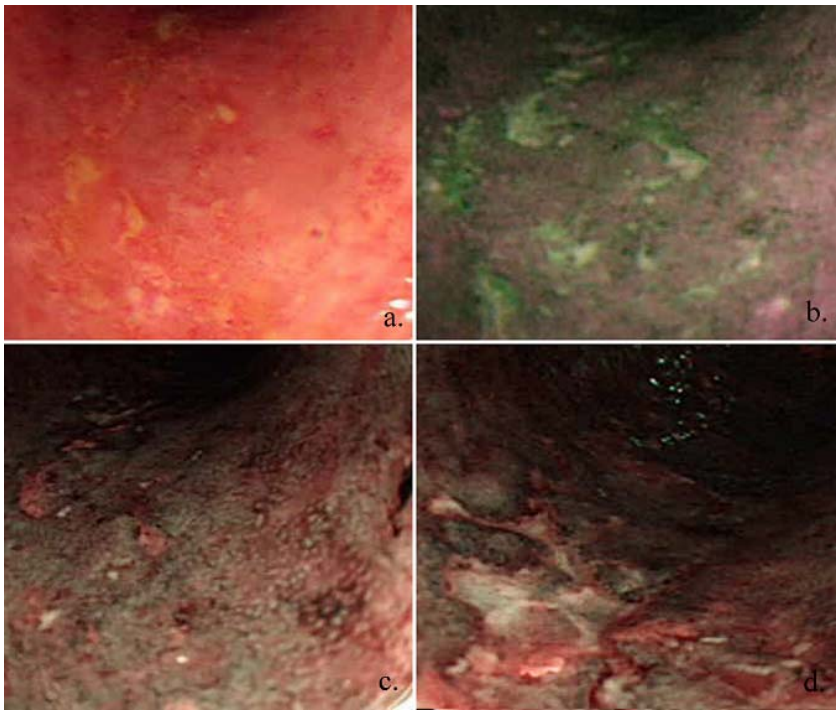

Figure 2. Active phase in UC: (a) superficial ulcerations, hyperemia of the mucosa and loss of vascular architecture seen with WLE; (b) fluorescent superficial ulcerations with defined circumferential margins seen with AFI; (c) inflamed mucosa with brownish areas and obscured blood vessels, and (d) ulcerations characterized by defects in the epithelium seen with NBI.

I-SCAN

I-SCAN is a digital contrast method that involves a post-processing algorithm applied on images obtained with WLE [28], resulting a real-time virtual image, without using optical filters. For this, the intensity of narrowed blue light is increased to a maximum and those of narrowed red and green light are decreased to a minimum. The new virtual image has an enhanced mucosal surface and better contrast of the capillary patterns [29].

I-SCAN technology offers three types of image enhancement: surface enhancement (SE), contrast enhancement and tone enhancement (TE). SE analyses the differences in luminance intensity between the pixels from the target area and those from surroundings, increasing light-dark contrast, which allows detailed observation of the lesion borders and mucosal surface structure. In contrast enhancement mode, the blue colour is digitally added to relatively dark areas, obtaining a higher luminance intensity that allows observation of the tiniest irregularities on the mucosa. TE deconstructs and analyses the individual RGB components of the colour spectrum, changing the colour frequencies of each component and reconstructing the components to a single, new coloured image. TE mode suppresses most of the dominant red and the image obtained has an elevated blue/green contrast which enables subtle mucosal abnormalities visualization. TE works in real time and has three modes: TE-g for gastric tumours, TE-c for colonic tumours and TE-e for oesophageal tumours. These algorithms are incorporated in three different modes: i-SCAN mode 1 uses SE and contrast enhancement, used to see details of the mucosal surface from depressed or elevated areas without altering the colour; i-SCAN mode 2 combines SE, contrast enhancement and TE-c allowing a better visualization of microvascularity and peripheral capillary network; i-SCAN mode 3 uses contrast enhancement, SE

and TE-g mode that improves the contrast between blood vessels and mucosa, creating a contrast-enhanced image, by maintaining the brightness. I-SCAN improves polyp characterization and visualizes the architectural subtleties in the mucosa [30-33] (Figures 3, 4).

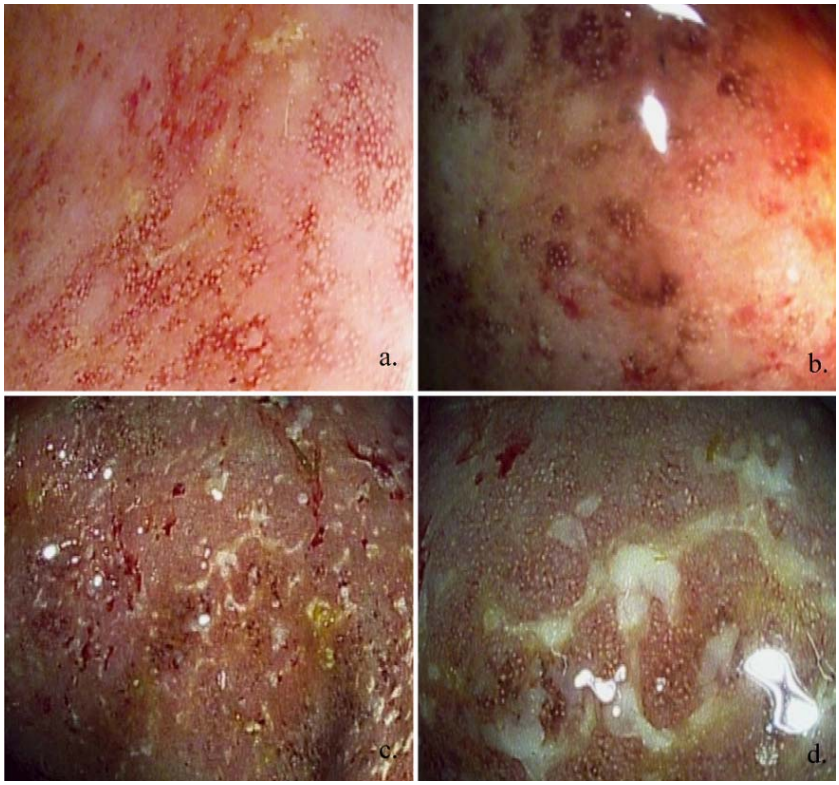

Figure 3. Patient with active CD, with serpiginous ulcerations and mucosal hyperemia (a. i-SCAN mode 1, b. i-SCAN mode 2, c. and d. i-SCAN mode 3).

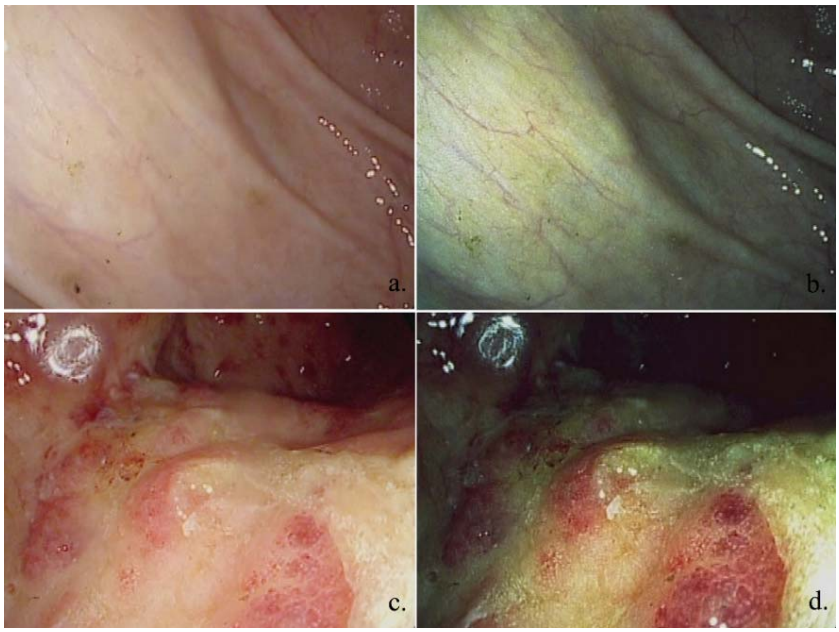

Figure 4. Patient with UC in active phase, with normal mucosa (a: WLE and b: i-SCAN mode 3) and inflamed mucosa with granularity, superficial ulcerations, hyperemia and loss of the vascular architecture (c) WLE and (d) i-SCAN mode 1.

FUJINON INTELLIGENT COLOR ENHANCEMENT

In Fujinon Intelligent Color Enhancement (FICE) system, by processing the reflected light from a surface, virtual images are reconstructed, using different wavelengths of red, green and blue signalling. The entire process is realised with computed spectral estimation technology [34, 35].

By modifying the white light to narrowed red, blue and green light, using an external software, real-time endoscopic images are reconstructed instantaneously. FICE chooses spectral images obtained from the wavelengths used and assigns them to the Red, Green and Blue monitor input channels. Also, it can vary the reflected wavelengths to display a variety of different images [35]. There are four different FICE patterns with different wavelength selections (FICE 1, 2, 3 and Blue). Immediately, an ordinary image can be switched to a FICE image by simply pressing a button on the endoscope. FICE 1 and 2 are used to better visualize the vascular structures [36, 37]. Depending on the wavelength applied, after processing the image, different reflection aspects of the mucosa are displayed. When FICE system is coupled with electronic or optical magnification, mucosal details are enhanced [37-39].

CONFOCAL LASER ENDOMICROSCOPY

Confocal laser endomicroscopy (CLE) is a real-time alternative to histology during endoscopy, allowing *in vivo* microscopic imaging of the mucosal layer [40]. A low-powered laser produces a blue light (with a wavelength of 488 nm) that is focused into a single point through an objective lens. Once the light reaches the tissue, a fluorescence signal returns back, being detected by the same lens, and passes through a pinhole. The scattered light does not pass through the pinhole and is excluded from detection, allowing an increased spatial resolution of the images obtained. The fluorescence signal is captured and converted into an imaging signal, that is further processed by a software system, resulting a whole image pixel-by-pixel and line-by-line. The final grey image obtained is from a variable depth of 0-250 μm and a 475 μm by 475 μm field of view, representing an optical section from one focal plane, within the examined structure [41-44]. To obtain the fluorescent signal, a contrast agent is needed [45]. The contrast agents used include acriflavine, fluorescein, cresyl violet and tetracycline. Acriflavine hydrochloride (e.g. 0.05% in saline, topical use only), which labels superficial epithelial cells including nuclei, and fluorescein sodium (e.g. 5 mL of a 10% solution, intravenous administration) that contrasts cellular and subcellular details, connective tissue and vessels architecture without staining nuclei, are mostly used [46, 47].

Currently there are two types of CLE: one integrated into the distal tip of a video endoscope, enabling confocal microscopy added to standard video endoscopy (eCLE – Pentax, Tokyo, Japan) and another as a stand-alone probe inserted through the working channel of most endoscopes (pCLE – Cellvizio, Mauna Kea Technologies, Paris, France) [48].

eCLE generates endoscopic and confocal images simultaneously [49]. This imaging system laser produces a blue light and detects fluorescence of 505-585 nm wave length. The scan rate for collecting CLE imaging data is 1.6 frames per second (1024 × 512 pixels) or 0.8 frames per second (1024 × 1024 pixels). The captured images have a field of view of 475 μm × 475 μm, a lateral resolution of 0.7 μm, an axial resolution of 7 μm. The depth levels are adjustable from 0 to 250 μm [45].

pCLE is a fibre optic probe which can be used with any endoscope with a working channel of at least 2.8 mm diameter [44]. The probe has a semiconductor laser that produces an excitation wavelength of 488 nm. All types of probes generate dynamic images at a scan rate of 12 frames per second with a 30 000 pixels scanning field. pCLE has a field of view of 240-600 μm with a lateral resolution of 1-3.5 μm. The depth level scanned is fixed and depends on the type of probe used. A special computer algorithm named "mosaicing" reconstructs the single video frames in an enlarged field of view image (~4 mm × 2 mm) [45] (Figure 5).

CLE can classify normal, regenerative and neoplastic tissue, by evaluating the crypts and vascular architecture (Tables 2, 3, 4) [49].

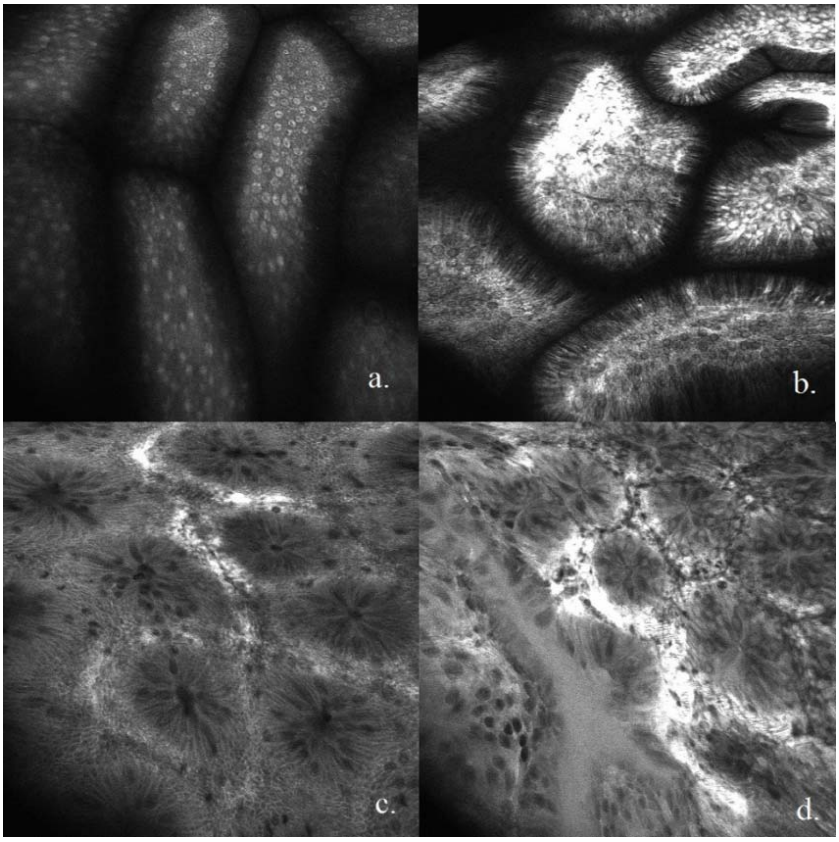

Figure 5. CLE of lower GI tract, 10% fluorescein sodium contrast agent is used: (a) normal ileum with longitudinal villi; (b) CD: ileitis, the inflammation is defined by increased quantity of fluorescein inside the villi which also no longer have a longitudinal aspect; (c) normal colon with round shaped crypts situated at equal distance one from another and thin and regular blood vessels; (d) UC: inflammation characterized by loss of crypt distance and shape, dilated blood vessels with increased fluorescein leakage.

Table 2
Microvascular architecture by eCLE assessment in UC

Vessel architecture	**Description**
Normal	Hexagonal or honeycomb appearance that represents a network of capillaries which outlines the stroma and surrounds the crypts luminal openings
Inflammation-regenerative	The hexagonal or honeycomb appearance is preserved, but it has a slight increase of capillaries number
Dysplastic	The vessels are dilated and distorted with increased leakage; the architecture is irregular with little orientation to the adjoining tissue or no orientation at all

Table 3
pCLE crypt and vessel architecture assessment in UC

Crypt architecture	Crypts are fusioned and distorted Bright epithelium
Vessel architecture	Dilated and prominent branching vessels

Table 4
Proposed CLE features to differentiate CD and UC [50]

Crohn's disease	**Ulcerative Colitis**
Mucosal fissures	Bifid crypts (lamina is double)
Focal cryptitis	Crypts are shortened and branched
Granulomas (if seen)	Distal progression of microscale inflammatory intensity
In the terminal ileum microscopic inflammation is present	The terminal ileum is microscopically intact

RESULTS

DYSPLASIA AND NEOPLASIA DETECTION

Chronic inflammation can initiate and sustain histologic and molecular changes that could occur in the intestinal epithelium and might lead to colorectal cancer. This process has an earlier histologic manifestation: dysplasia, which is an important factor for CRC prevention if discovered in time [51].

Several imaging techniques have been tested to establish which one is the most suitable for dysplasia/neoplasia detection.

CE with indigo carmine or methylene blue demonstrated its utility in a six randomized controlled trials meta-analysis. The pooled sensitivity was 83.3% and specificity 91.3% for the diagnosis of dysplastic lesions in UC [52]. In a similar study of 100 patients with UC, dysplasia detection was increased by using CE with indigo carmine ($p = 0.06$), compared to conventional colonoscopy. Targeted biopsies (taken from dyed areas) detected dysplasia in significantly more patients ($p = 0.02$) than nontargeted ones [53].

In a report of 165 patients with UC, randomized to conventional colonoscopy or colonoscopy with CE using methylene blue [12], CE could differentiate neoplastic changes from non-neoplastic ones with a sensitivity and specificity of 93%. CE predicted colonic inflammation ($P = 0.0002$) significantly better than conventional endoscopy, as well as the extent (89% *vs*. 52%; $P < 0.0001$) of active UC. However, in a recent study where 440 CE were performed in 401 patients and 1802 WLE in 772 patients, dysplasia detection was not increased by the use of CE instead of WLE with targeted/random biopsies. In the CE group dysplasia was identified during 48 surveillance procedures and in WLE group in 189 procedures (11% *vs*. 10%; $p = 0.80$). In the CE group, targeted biopsies detected 59 dysplastic lesions and in the WLE group, 211 lesions ($P = 0.30$) [54].

A more recent study carried out on 44 patients with UC compared the results obtained with both CE and NBI [55]. More nondysplastic ($P < 0.001$) and neoplastic lesions were identified with CE than NBI ($P = 0.180$). Nevertheless, NBI Kudo assessment for dysplasia had low sensitivity (42%) and modest accuracy (74%). In another study comparing NBI with CE for intraepithelial neoplasia detection in long-standing IBD, NBI was less time-consuming, but equally effective as CE ($p < 0.1$). However, the authors concluded that NBI cannot be recommended as a standard technique for IBD surveillance [56].

Another study based on neoplasia detection compared NBI with WLE on 42 patients with UC. NBI detected 52 suspicious lesions in 17 patients, compared to 28 lesions in 13 patients, for WLE. Targeted biopsies with histopathological evaluation revealed neoplasia on 11 patients, 4 patients were diagnosed by both methods, other 4 patients with NBI and 3 patients with WLE ($P = 0.705$). The authors concluded that the 2 techniques are comparable; although NBI detected more lesions, they still recommend random biopsies during UC surveillance [57].

AFI seemed to prove its role in a study of 48 patients with UC, aimed to examine protruding lesions and flat areas for dysplasia diagnosis. A higher rate of dysplasia was detected in protrusions (31%) compared to flat mucosa (3.3%, $P < 0.0001$) and the frequence of dysplasia was significantly higher in low autofluorescence than in high autofluorescence protruding lesions (45.0% *vs*. 13.3%, $P = 0.043$) [58].

In a study of 50 patients with UC that underwent surveillance colonoscopy with endoscopic trimodal imaging (WLE, AFI, NBI), the AFI miss-rate for detecting neoplasia was 0% while for WLE it was 50% ($p = 0.036$). Using AFI, all neoplastic lesions were coloured purple (sensitivity 100%). AFI did improve neoplasia detection, instead NBI and pit pattern analysis had only moderate accuracy for histology prediction [59].

Another study was conducted on 95 patients with longstanding UC, to determine the accuracy of high definition (HD) WLE, CE with indigo-carmine and i-SCAN, in dysplastic lesions (DL) detection. Three groups were created HD (33.7%, $n = 32$), CE (34.7%, $n = 33$) and i-SCAN (31.6%, $n = 30$). Totally, 47 lesions were found, 30 (63.8%) in HD group (specificity = 89.29%, sensitivity = 86.67%, NPV = 86.21% and PPV = 89.66%), 6 in CE group (12.8%) (specificity = 88.57%, sensitivity = 66.67%, NPV = 93.94%, PPV = 50%) and 11 in the i-SCAN group (23.4%) (specificity = 83.3%, sensitivity = 100%, NPV = 100%, PPV = 64.71%). HD did detect the majority of DL, which might support it as the method of choice in IBD surveillance [60].

Regarding CLE, Kiesslich R. *et al*. compared WLE (73 patients) and CE combined with CLE (80 patients) in a study carried out on 161 patients with long-standing UC (8 patients have been excluded). 4.75-fold more neoplastic lesions were detected in CE-CLE group ($P = 0.05$). CLE could predict neoplastic changes with high accuracy: sensitivity, specificity and accuracy were 94.7%, 98.3% and 97.8% [61]. A similar study was realised on

51 patients with long-standing UC. CE and CLE were used on 14 (27%) patients with macroscopic suspected dysplasia and 5 cases were confirmed by histology to have dysplasia. CLE diagnostic accuracy for dysplasia detection *versus* histology was: specificity 90%, sensitivity 100%, PPV 83% and NPV 100% [62]. The conclusion was that CLE associated with CE might significantly improve the UC management.

MUCOSAL HEALING AND INFLAMMATION ASSESSMENT

Inflammation and clinical activity are important issues for patients' management. Mucosal healing (MH) became a measure for disease activity in IBD, being characterized by the complete absence of inflammation, erosions or ulcerations [63].

A recent study that assessed MH in UC using magnifying CE (MCE), was carried out on 30 patients with quiescent disease that had MH on WLE (Mayo score 0). Four magnifying subscores were used: 0 – similar to normal mucosa, 1 – disarray of crypts and fine network, 2 – crypts without pit pattern, fine network pattern fusioned or disrupted, and 3 – crypts and fine network patterns completely disorganized/disappeared. Two groups of patients were created: one without relapse (subscores 0 and 1) and another with clinical relapse (subscores 2 and 3). At 12 months after MCE, the relapse-free group was significantly higher (89.5%) when compared with the relapse group (36.4%) ($p < 0.01$). The conclusion was that MCE can improve MH assessment [64].

AFI was evaluated in a study on 42 patients with UC aimed to determine its clinical relevance for inflammation evaluation. 572 images were taken from the same area during endoscopy, 286 with WLE and 286 with AFI. In WLE images, inflammation was assessed according to 7 endoscopic features and Mayo subscore, and in AFI images according to blue, green and red colour components (based on an RGB color model). The scores from both types of image (from the same area) were compared. The relative to green colour ($P < 0.01$; $r = -0.62$) was associated with inflammation rather than blue ($P < 0.01$, $r = 0.56$) or red ($P < 0.01$, $r = 0.52$). The components analysed for WLE images like edema ($P < 0.01$, $r = -0.62$), vascular pattern ($P < 0.01$, $r = -0.65$), crypt architectural irregularities ($P < 0.01$, $r = -0.51$) were correlated with the AFI green colour. Also, the endoscopic features and histology correlated with the AFI green colour component. AFI can assess microscopic inflammation in UC if the green colour component is used as a disease activity criterion [65].

Another study used NBI to visualize intestinal angiogenesis in 14 patients with IBD, which appears in both inflammation and cancer. There was a significant ($P < 0.05$) increase of angiogenesis in normal WLE areas and NBI positive. A significant ($P < 0.01$) increase in vessel density was also seen in inflamed areas observed with WLE and NBI positive compared with NBI negative areas [66].

In a study of 50 patients with IBD, i-SCAN correctly identified disease severity and extent in mild or inactive disease. Compared with histology, i-SCAN characterised the mucosal inflammation more precisely ($P < 0.05$) than WLE [67].

A more recent study used i-SCAN for the assessment of mucosal healing in UC patients. 45 patients were examined with i-SCAN and WLE. For each patient, the Mayo endoscopy subscore was calculated using WLE, targeted biopsies and histology grading, according to the Harpaz score. There was a strong correlation between i-SCAN scores of mucosal and vascular patterns, and Mayo ($rs = 0.802$; $p < 0.00001$) and Harpaz subscores ($rs = 0.6702$; $p < 0.00001$) [68].

In one study that used double-ballon enteroscopy with FICE technology to assess patients with CD, FICE added little to WLE detection of ulcers and erosions [69].

CLE was used in a study to assess MH by evaluating the crypt number and architecture, before and after the start of anti-TNF-alpha therapy in CD and UC. Patients with active UC (17; Mayo > 6) and active CD (14; CDAI > 220) underwent colonoscopy with CLE before and after 3 infliximab infusions. In the responder group, the differences between pre- and post-treatment scores were statistically significant ($p < 0.05$), in contrast to the non-responder group ($P > 0.05$). The authors concluded that CLE can accurately assess MH *in vivo* [70].

Another study evaluated CLE capacity to predict clinical relapse in 43 patients with UC. CLE assessed the mucosa of each patient's sigmoid and rectum before taking targeted biopsies. The patients were followed up (at least 12 months) to determine the relapse, based on the Simple Clinical Colitis Activity Index. The CLE specificity, sensitivity, and accuracy for active inflammation diagnosis in real-time were 85%, 95.7% and 90.7%. CLE was comparable to histology [71].

SURVEILLANCE – GUIDELINES

The international consensus statement (SCENIC – 2015) on IBD surveillance recommends high definition (HD) WLE instead of standard definition (SD) WLE, and CE instead of WLE. It also recommends performing a pan-colonic CE with targeted biopsies from any visible lesion [72].

AFI and NBI or I-SCAN and FICE are not currently recommended in IBD surveillance [72, 73].

Also, CLE is not included in guidelines, because it cannot be used to examine the entire colon (as it is recommended in IBD surveillance). It might have a utility to characterize a lesion discovered during surveillance.

Regarding random biopsies, they are recommended when HD WLE is used. Targeted biopsies are required only when CE is used to detect dysplasia on a visible lesion.

CONCLUSIONS

A detailed analysis of the studies published to date supports the utility of CE in IBD surveillance, particularly in identifying early stages of carcinoma and dysplastic lesions that are not visible with conventional WLE. Moreover, CE is currently recommended by guidelines in IBD patients' surveillance.

AFI studies concluded that it is useful for taking targeted biopsies, but it does not increase the diagnosis accuracy.

Regarding NBI, although it is less time-consuming than CE, it is not recommended as a surveillance method instead of CE.

Concerning FICE and i-SCAN, there are not enough studies to determine whether they have a major contribution in assessing patients with IBD. One big advantage is that these 2 techniques are not time-consuming and can be easily used on any suspicious lesion, for targeting biopsies, without the need of stain agents.

CLE, consisting of *in vivo* histologic examination, has its utility in evaluating any visible lesion, although it requires a thoroughly trained endoscopist, with support from an equally trained pathologist. The technique helps to decrease the number of untargeted biopsies through a microscopic assessment of the mucosa. Maybe, more important, CLE can impact clinical management algorithms as it could assess mucosal healing and consequently direct endoscopic exit strategies for IBD patients under biological treatment.

Present data does not support with certainty the efficacy or inefficacy of any of these techniques, except for CE, which has already been included in guidelines for IBD surveillance.

As a final conclusion, more studies are needed to see which other technique might be useful in evaluating patients with IBD.

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Introducere. *Boala Crohn şi colita ulcerativă sunt boli inflamatorii intestinale (IBD) asociate cu riscul apariţiei cancerului colorectal, la pacienţii cu evoluţie îndelungată. Pentru a putea examina mucoasa colonului şi a putea descoperi leziuni displazice sau neoplazice, sunt necesare tehnici endoscopice avansate. Asemenea tehnici sunt detaliate în review: cromoendoscopia (CE), imagistica bazată pe autofluorescenţă (AFI), imagistica cu bandă îngustă (NBI), i-SCAN, Fujinon Intelligent Color Enhancement (FICE) şi endomicroscopia confocală laser (CLE).*

Scop. *Scopul acestui review este de a descrie şi a stabili impactul clinic al tehnicilor endoscopice avansate ce ar putea fi folosite în examinarea pacienţilor cu IBD pentru evidenţierea vindecării mucoasei, inflamaţiei microscopice, displaziei sau neoplaziei.*

Material şi metode. *A fost realizată o cercetare în literatura electronică despre noile metode imagistice folosite pentru evaluarea pacienţilor cu IBD.*

Rezultate. *De-a lungul timpului au fost realizate multiple studii axate pe determinarea utilității tehnicilor imagistice în urmărirea pacienților cu IBD. În ceea ce priveşte descoperirea displaziei sau a neoplaziei, a vindecării mucoasei sau a inflamației microscopice, CE a demonstrat că este superioară endoscopiei clasice, în timp ce NBI şi AFI nu au avut rezultate încurajatoare. I-SCAN nu a adus îmbunătățiri calității colonoscopiei, în timp ce FICE a fost folosit în prea puține studii. CLE poate fi folosit pentru a analiza o leziune, având aceleaşi rezultate ca şi studiul histopatologic.*

Concluzii. *În acest moment, CLE este singura tehnică imagistică recomandată de ghidurile internaționale pentru urmărirea pacienților cu IBD. CLE poate fi folosit pentru a caracteriza o leziune deja descoperită în timpul endoscopiei clasice. Celelalte tehnici necesită mai multe studii pentru a putea trage concluzii referitor la eficiența sau ineficiența acestora.*

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