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Review

Advanced endoscopic imaging for diagnosis of inflammatory bowel diseases: Present and future perspectives

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Crohn's disease and ulcerative colitis are chronic inflammatory bowel diseases (IBD) causing severe damage of the luminal gastrointestinal tract. Differential diagnosis between both disease entities is sometimes awkward requiring a multifactorial pathway, including clinical and laboratory data, radiological findings, histopathology and endoscopy. Apart from disease diagnosis, endoscopy in IBD plays a major role in prediction of disease severity and extent (i.e. mucosal healing) for tailored patient management and for screening of colitis-associated cancer and its precursor lesions. In this state-of-the-art review, we focus on current applications of endoscopy for diagnosis and surveillance of IBD. Moreover, we will discuss the latest guidelines on surveillance and provide an overview of the most recent developments in the field of endoscopic imaging and IBD.

Key words: advanced imaging, BLI, IBD, LCI, NBI

INTRODUCTION

BOTH CROHN 'S DISEASE and ulcerative colitis are chronic inflammatory bowel diseases (IBD) causing severe damage of the luminal gastrointestinal tract. Differential diagnosis between both disease entities is sometimes awkward including a multifactorial pathway, containing clinical and laboratory data, radiological findings, histopathology and endoscopy.[1] Apart from disease diagnosis, endoscopy in IBD plays a major role in prediction of disease severity and extent (i.e. mucosal healing) for tailored patient management and for screening of colitis-associated cancer and its precursor lesions.

Patients with both Crohn's disease and ulcerative colitis are at increased risk of developing colorectal cancer (CRC). A large meta-analysis described a cumulative incidence for CRC of 2% at 10 years, 8% at 20 years and 18% after 30 years of disease.[2] Therefore, surveillance is recommended, starting in all patients at 8 years with restaging biopsies and every 1–3 years.[3] Presence of specific risk factors, including active inflammation, anatomical abnormality (stricture, multiple pseudopolyps), history of dysplasia, family history of CRC in first-degree relatives and primary sclerosing cholangitis (PSC) merits annual surveillance intervals. As dysplasia in IBD is often flat and unequivocal, guidelines recommend obtaining at least 32 random biopsies from all segments of the colon.[4] However, most recent data have shown that the approach of random biopsies is not effective. In a retrospective analysis of 1010 colonoscopies, van den Broek *et al.* measured the neoplasia yield per colonoscopy and the clinical impact per patient of random biopsies. Four hundred and sixty-six colonoscopies were carried out for surveillance during which 11 772 random biopsies were taken (median 29). Overall, neoplasia was detected in 88 colonoscopies, in 85% by targeted biopsies only and in 9% by both targeted and random biopsies. Notably, neoplasia was detected in random biopsies in only four patients. Of note, two of these patients had visible neoplasia in previous colonoscopies. Therefore, the yield of random biopsies was considerably low whereas neoplasia was macroscopically visible in up to 94% of colonoscopies.[5] Most recently, Watanabe *et al.*[6] presented the results of a randomized controlled trial carried out at 52 institutions in Japan comparing rates of neoplasia detection by targeted versus random biopsies in patients with ulcerative colitis. Patients were randomly assigned to undergo four random biopsies collected every 10 cm in addition to targeted biopsies or targeted biopsies from

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locations of suspected neoplasia only. Neoplasia was detected in 11% of patients in the target group and in 9% of patients in the random group which was not statistically significantly different. However, significantly more biopsies per colonoscopy were collected in the random group (35 *vs* 3), and even the total examination time was longer (42 *vs* 27 min). Therefore, the targeted biopsy approach appears to be non-inferior to random biopsies but more cost- and time-effective.

Taking the above into consideration, it appears obvious that there is a strong need for innovation in the field of endoscopy in IBD. In this state-of-the-art review, we are therefore focusing on current applications of endoscopy for diagnosis and surveillance of IBD. Moreover, we will discuss the latest guidelines for surveillance in IBD and provide an overview of the most recent and future developments in the field of endoscopic imaging and IBD.

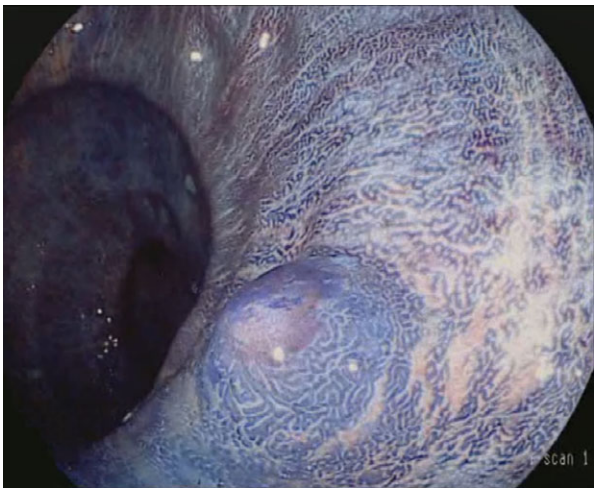

Figure 1 Traditional chromoendoscopy in inflammatory bowel diseases. Panchromoendoscopy, as in this case with methylene blue, allows for identification of subtle mucosal lesions.

TRADITIONAL APPROACH: DYE-BASED CHROMOENDOSCOPY

THE PRINCIPLE OF staining to enhance mucosal surface pattern morphologies goes back to the 1990s and therefore represents one of the oldest techniques in endoscopic imaging.[7] The principle of dye-based chromoendoscopy, however, still remains the same. Biocompatible dyes are given through the working channel of an endoscope followed by careful inspection of the mucosa for suspicious lesions (Fig. 1). Once a lesion is identified, endoscopic resection should be carried out as redundant biopsies are causing severe fibrosis, thereby impeding endoscopic resection strategies.[8] Biopsies should only be taken from lesions which appear unresectable or after resection from the area surrounding the lesion in order to rule out additional dysplasia.

One more recently introduced meta-analysis showed a significant increase in patients with dysplasia when chromoendoscopy was used, resulting in an absolute increase of 8%. In addition, the total number of dysplastic lesions was increased with chromoendoscopy.[9] These data have been seen when both standard definition and high-definition imaging were compared to chromoendoscopy.

As evidence is suggesting that in the era of modern endoscopy, most dysplasia in IBD are visible and random biopsies are not effective in the early detection of dysplasia, the most recently introduced international consensus statement provides recommendations on surveillance and management of dysplasia in IBD.[9] The SCENIC statement provides clear evidence that chromoendoscopy rather than white-light endoscopy (including both standard and high-definition imaging) is suggested, but also that dye-less chromoendoscopy techniques, as discussed in the next paragraph, are currently not recommended to replace the approach of traditional dye-spraying. Moreover, the consensus recommends that for patients with endoscopically invisible dysplasia, confirmed by a gastrointestinal pathologist, referral to an endoscopist with expertise in IBD surveillance using chromoendoscopy with high-definition colonoscopy is suggested.

The consensus also provides staining recommendations for both lesion detection and lesion characterization in IBD patients. For lesion detection, panchromoendoscopy with either indigocarmine (0.03%) or methylene blue (0.04%) with the dyes applied through a water jet channel or biopsy channel is recommended. For lesion characterization and delineation of borders, targeted chromoendoscopy is recommended with either indigocarmine (0.13%) or methylene blue (0.2%) applied with syringe spray through the biopsy channel.

Although effective, potential limitations of traditional chromoendoscopy need to be discussed.[10] Chromoendoscopy prolongs the endoscopic examination significantly by a mean of 11 min. Moreover, a distinct learning curve is required and there are additional costs for dye spraying, associated with a lack of reimbursement, limiting the wide application of the technique outside specialized centers.

OPTICAL CHROMOENDOSCOPY IN IBD

TO DATE, VARIOUS optical chromoendoscopy systems are available, consisting of narrow band imaging NBI

(Olympus, Tokyo, Japan), i-scan OE (Pentax, Tokyo, Japan), CBI (Aohua Photoelectricity, Shanghai, China) and VIST (Sonoscape, Shenzhen, China). Optical chromoendoscopy uses an optical filter placed after the light source, typically in order to narrow the red light, thereby enhancing the mucosal vascular pattern morphology.[11] To date, only data for the NBI system for dysplasia detection are available. However, as all technologies are using a similar technique, one can potentially anticipate comparable results for all.

Recently, a prospective, randomized, cross-over study of 42 patients with long-standing ulcerative colitis compared NBI with conventional colonoscopy for detection of dysplasia.[12] With NBI, 52 suspicious lesions were detected in 17 patients, compared with 28 suspicious lesions in 13 patients detected during conventional colonoscopy. Targeted biopsies showed 11 patients with neoplasia. In four patients, neoplasia was detected by both techniques; in an additional four patients, neoplasia was detected by NBI only, and in three patients, only by conventional white-light endoscopy. Of note, out of 1522 random biopsies carried out, only one additional patient with dysplasia was diagnosed.

These data were also confirmed by other randomized controlled studies[13,14] while similar results have been shown when NBI was compared to chromoendoscopy. Most recently, Bisschops *et al.*[15] carried out a prospective randomized controlled trial comparing the performance characteristics of both techniques in patients with long-standing ulcerative colitis. Overall, no significant difference was found for neoplasia detection between NBI and chromoendoscopy with a mean number of neoplastic lesions per colonoscopy of 0.47 for chromoendoscopy and 0.32 for NBI. Per-lesion analysis indicated neoplasia detection of 17% for chromoendoscopy and 16% for NBI.

Recently i-scan OE was evaluated for assessment of inflammatory changes in ulcerative colitis.[16,17] The diagnostic accuracy of i-scan OE was calculated against histology using two specific histological scoring systems. Overall, i-scan OE showed a significant correlation with histology. Of note, the majority of patients with Mayo grade 0 also showed mucosal abnormalities on i-scan OE. Future research is currently focusing on the potential of advanced endoscopic imaging techniques for prediction of disease severity and extent in IBD and the results of large-scale multicenter trials are highly anticipated.

DIGITAL CHROMOENDOSCOPY IN IBD

DIGITAL CHROMOENDOSCOPY TECHNIQUES are based on computed spectral estimation technologies. Accordingly, no optical filters are required. Various techniques are available such as Flexible spectral Imaging Colour Enhancement (FICE) (Fujifilm, Tokyo, Japan), i-scan (Pentax) and Storz Professional Image Enhancement System (SPIES) (Storz, Tuttlingen, Germany).

No data are yet available on the usefulness of digital chromoendoscopy techniques for dysplasia detection in IBD, although the results of large-scale randomized controlled trials are anticipated.

Two studies have addressed the value of digital chromoendoscopy for prediction of disease severity and extent (i.e. mucosal healing) in IBD. In one study, 78 consecutive patients with IBD were randomly assigned in a 1:1 ratio to undergo colonoscopy with high-definition white-light or i-scan. Digital chromoendoscopy correlated significantly better with histology for both prediction of disease extent and severity than white-light imaging.[18] The second study assessed 78 patients with ulcerative colitis by i-scan and white-light endoscopy.[19] It was found that subtle histological abnormalities underlying the apparently healed mucosa in ulcerative colitis could be detected using digital chromoendoscopy in the majority of patients with seemingly complete mucosal healing.

Future studies are now evaluating whether a more aggressive therapy of IBD patients in the quiescent or mild phase of the disease might reduce further disease progress and relapse.

NEW LIGHT FOR IBD: LIGHT-EMITTING DIODE AND LASER OPTICS

APART FROM XENON light sources, most recently introduced technologies are using laser-based emission systems (Blue Laser Imaging; Fujifilm) or light-emitting diode (LED) optics (Blue Light Imaging and Linked Color Imaging, both Fujifilm) to enhance mucosal surface and vascular pattern morphologies[20] (Figs 2 and 3).

Only one case report has yet described the feasibility of linked color imaging technology (LCI) for diagnosis of ulcerative colitis-associated colorectal cancer.[21] However, one most recently published manuscript evaluated the efficacy of LCI for diagnosing mucosal inflammation in ulcerative colitis patients.[22] Among areas with Mayo endoscopic subscore of 0, LCI technology significantly improved the diagnosis of residual inflammation and was strongly correlated with the histopathological Matts score. Of note, non-relapse rates also significantly correlated with LCI classification, but not with the Mayo endoscopic subscore.

Therefore, LCI may serve as a novel approach for evaluating colonic mucosal inflammation and for prediction of clinical outcomes in IBD patients.

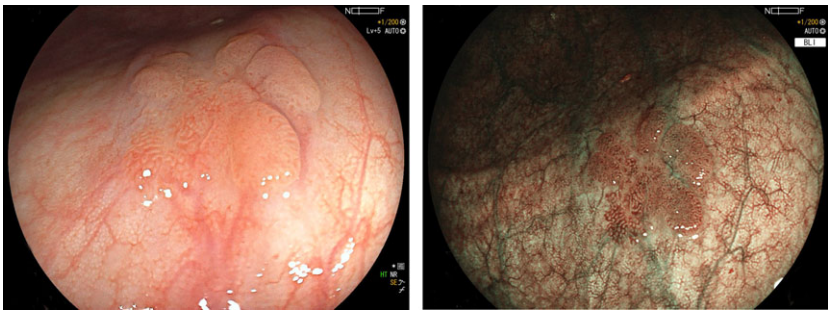

Figure 2 Comparison of high-definition white-light imaging and blue light imaging (BLI) for characterization of non-polypoid colorectal lesion. BLI is enhancing the mucosal vascular pattern morphology, thereby allowing enhanced characterization and delineation of the lesion.

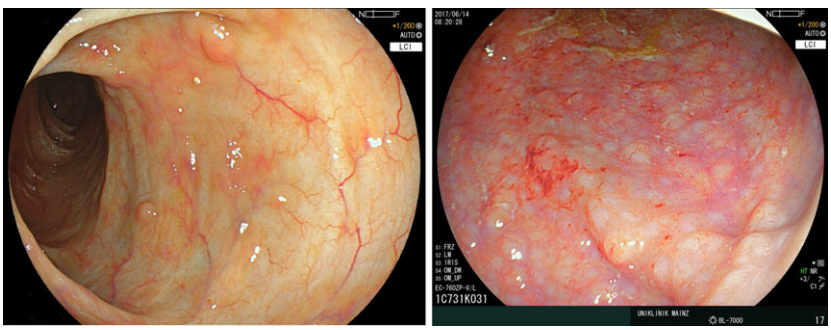

Figure 3 Linked color imaging (LCI) in ulcerative colitis. Contrary to optical chromoendoscopy techniques LCI is enhancing red and white contrast, thereby improving visibility without changing the natural color of the tissue.

ENDOPATHOLOGY AND COMPUTER-ASSISTED DIAGNOSIS

THE TERM "ENDOPATHOLOGY" was introduced many years ago and is now mostly used in relation to confocal laser endomicroscopy and endocytoscopy. Both techniques allow for extensive magnification of the mucosal surface in real time and are therefore not used for detection, but are more suitable for characterization of lesions.

Technological details of both techniques have been described in detail elsewhere and are not the scope of the present review[23,24] (Fig. 4).

Confocal laser endomicroscopy

Early data have shown that chromoendoscopy in conjunction with confocal imaging allows for 4.75-fold more neoplasia to be found compared to conventional white-light endoscopy, although up to 50% fewer biopsies were required.[25]

Moreover, recent data have highlighted the potential role of confocal imaging for real time *in vivo* prediction of histological changes associated with intestinal disease activity. In this context, it has been shown that assessment of crypt architecture and fluorescein leakage showed good correlations with histological results.[26] Of note, half of the patients with normal mucosa seen on conventional white-light endoscopy showed acute inflammation on histology, whereas no patients with normal mucosa or with chronic inflammation seen on confocal imaging showed acute inflammation on histology. Similar results have also been shown for patients suffering from Crohn's disease.[27] More recent evidence has also highlighted the potential of confocal imaging for the differential diagnosis of ulcerative colitis and Crohn's disease.[28] In a prospective study, Crohn's patients showed significantly more frequently discontinuous inflammation, focal cryptitis and discontinuous crypt architectural abnormality than patients with ulcerative colitis. Conversely, ulcerative colitis was more often associated with severe, widespread crypt distortion, decreased crypt density and a frankly irregular surface.

Confocal imaging has also been evaluated for prediction of disease relapse and clinical outcome in IBD. Buda *et al.* first described that patients with inactive disease showed a

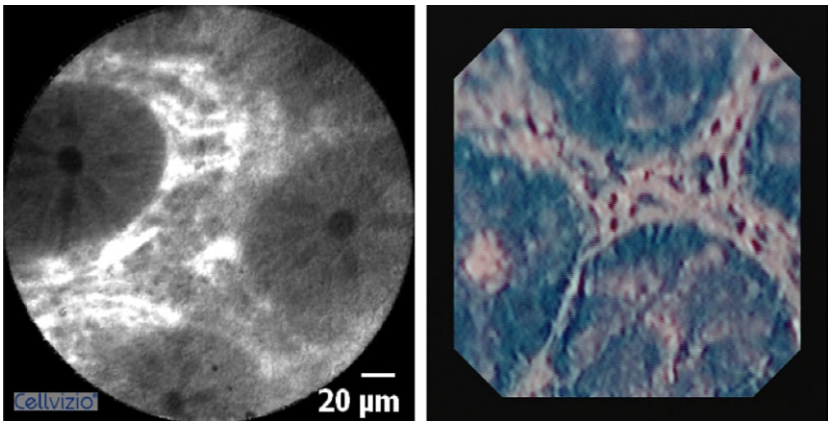

Figure 4 Confocal laser endomicroscopy and endocytoscopy both allow for tissue analysis at the cellular level. Confocal imaging is more restrictive to architectural details whereas endocytoscopy allows for both characterization of cellular details and vascular pattern.

significant increase in fluorescein leakage, crypt diameter and inter-crypt distance compared to patients with quiescent disease. Based on these findings, the authors composed an outcome score and were able to predict disease flare during a 12-month follow-up period.[29]

Most recently, our group has shown that focal cryptitis and crypt architectural abnormalities are frequently observed in Crohn's patients.[30] These patients showed an increased incidence of medical treatment escalation and transmural lesions at 1-year follow up. Confocal imaging showed specific features of mucosal inflammation and allowed for early prediction of relevant clinical outcome parameters.

Further studies should now address whether this promising prognostic tool could refine the timing of treatment strategies in patients with Crohn's disease.

More data have also highlighted the role of functional tissue diagnosis in IBD based on confocal imaging. First described in 2007, epithelial gap density in IBD has meanwhile emerged as an important factor allowing for prediction of disease relapse but also for prediction of hospitalization and surgery in patients with IBD.[31]

Confocal endomicroscopy was recently carried out in IBD and control patients to determine the relationship between cell shedding and local barrier dysfunction.[32] Most importantly, patients in clinical remission showing increased cell shedding were at increased risk of disease relapse within 12 months. Sensitivity, specificity and accuracy for predicting a flare were 63%, 91% and 79%, respectively, and cell shedding could therefore serve as a potential diagnostic tool for the management of IBD.

Similarly, Turcotte *et al.*[33] prospectively followed IBD patients for clinical events including symptom flares, medication changes, hospitalization, or surgery. Patients with elevated gap density were at significantly higher risk of hospitalization or surgery and gap density was identified as a significant predictor for risk of major events.

More recently, Chang *et al.*[34] carried out a prospective study of intestinal permeability, measured by confocal imaging in 110 consecutive subjects with IBD and 22 healthy control patients. Patients with symptomatic IBD had a significantly higher median confocal leak score than patients with asymptomatic IBD or controls. Overall, 36% of patients with IBD in mucosal healing were diagnosed with increased intestinal permeability. Interestingly, an increase in intestinal permeability correlated with increased severity of diarrhea. Therefore, mucosal permeability beyond mucosal healing might improve further outcomes of patients with IBD.

Endocytoscopy

Endocytoscopy has been studied in 40 patients with IBD and allowed for detection and discrimination of single mucosal inflammatory cells and inflammatory disease activity.[35] Interobserver agreement between two investigators was substantial (kappa: 0.61–0.78), whereas intraobserver agreement was substantial to almost perfect (kappa: 0.76–0.88). Concordance between endocytoscopy and histopathology for grading intestinal disease activity was measured as 100%. In a pilot study including 26 patients with ulcerative colitis, Nishiyama *et al.*[36] showed a correlation between endocytoscopy imaging and Matts' histopathological grade. In the study, patients were classified into two groups: those with an endocytoscopy score 0–2 (Grade A) and those with an endocytoscopy score of 3–6 (Grade B). With an average post-endocytoscopy

surveillance period of 446 days, only patients with grade B relapsed. Therefore, endocytoscopy imaging might become a predictive indicator for relapse of patients with ulcerative colitis although these initial data need to be confirmed in a larger cohort setting.

Using endocytoscopy, Nakazato *et al.*[37] recently assessed histological healing in 64 ulcerative colitis patients in clinical and endoscopic remission. They found that endocytoscopy can be used to assess histological healing in patients with ulcerative colitis without the need for biopsy specimens.

Although both confocal imaging and endocytoscopy allow for prediction of ultrastructural (i.e. histological) mucosal changes, interpretation of findings still requires special expertise and training in the field of histopathology.

Computed assisted diagnosis (CAD) has recently been developed in conjunction with endocytoscopy, thereby facilitating interpretation of findings.[38,39] Although CAD has yet only been established for colorectal polyps and invasive colorectal cancer, it is eventually anticipated that the CAD algorithm will allow for automated classification of surface and vascular pattern morphology in IBD patients.

PERSONALIZED MEDICINE AND MOLECULAR IMAGING

NOWADAYS, MEDICAL MANAGEMENT of patients suffering from IBD is evolving toward a personalized model. Therefore, definition of targets that guide intensification of therapy is highly warranted.[40] In this context, molecular endoscopic imaging (i.e. *in vivo* immunohistochemistry) is now rapidly evolving, potentially allowing for risk stratification, planning and guidance of therapy, monitoring therapeutic efficacy and assessing disease recurrence. Molecular imaging is based on topical or intravenous application of specific structures, including antibodies, peptides, lectins, small molecules or nanoparticles. Typically labeled with fluorescein isothiocyanate (FITC), simultaneous confocal imaging allows for specific identification of targeted structures such as membrane-bound receptors. Recent data have already highlighted the potential of molecular endoscopic imaging for *in vivo* diagnosis of Barrett's esophagus and colorectal polyps.[41,42] In addition to these studies, in 25 patients with Crohn's disease, our group has shown that topical administration of a fluorescent-labeled antibody for molecular *membrane* tumor necrosis factor (mTNF) imaging led to detection of intestinal mTNF (+) immune cells during confocal imaging.[43] Patients with high numbers of mTNF(+) cells showed significantly higher short-term response rates (92%) at week 12 upon subsequent anti-TNF therapy as compared to patients with low amounts of mTNF(+) cells (15%). Of note, the clinical response in the mTNF(+) patients was sustained over a follow-up period of 1 year and was associated with mucosal healing observed at follow-up endoscopy.

These initial data indicate that molecular endoscopic imaging with fluorescent-labeled antibodies is feasible and also has the potential to predict therapeutic responses to biological treatment and can therefore potentially be used for personalized medicine in IBD. Although these initial data need to be confirmed, they already provide the first evidence of the potential of molecular endoscopic imaging for personalized patient care and individual patient management.

CONCLUSION

MANAGEMENT OF IBD as a life-long disease is still challenging. The introduction of advanced endoscopic imaging techniques has led to an adaption of current guidelines. Most dysplasia in IBD is visible and therefore the recommendation for random biopsies during surveillance appears obsolete. Instead, high-definition endoscopes should be used in conjunction with traditional dye-spraying.

Table 1 Summary of potential advantages and disadvantages of endoscopic imaging in inflammatory bowel diseases

Technique	Dysplasia detection	Prediction of mucosal healing	Prediction of clinical outcome	Prediction of relapse	Prediction of therapeutic response
White-light	+	–	–	–	–
Traditional chromoendoscopy	++	–	–	–	–
Optical chromoendoscopy	–	+	–	–	–
Digital chromoendoscopy	–	+	–	–	–
LED-based imaging	–	+	–	+	–
Confocal imaging	+	++	++	++	–
Endocytoscopy	–	++	–	+	–
Molecular imaging	–	–	–	–	+

(++) good evidence; (+) weak evidence; (–) not effective; no data.

Although it might appear surprising that modern image-enhanced endoscopy systems are not able to improve dysplasia detection in IBD, one might explain this finding with the technical principle of dye-less chromoendoscopy techniques. The principle of these techniques mostly relies on visualization of mucosal vascular pattern morphology. However, in IBD, the vascular pattern morphology is generally disturbed by chronic inflammation. Therefore, it might appear obvious that technologies enhancing vascular pattern morphology for detection of dysplastic lesions are not effective in chronic inflammatory conditions. On the contrary, new LED-based systems have now been introduced, focusing more on general contrast enhancement of the luminal gastrointestinal tract. Data regarding the effectiveness of this new technology for enhanced dysplasia detection in IBD are therefore highly warranted.

In the rare case of patients with endoscopically invisible dysplasia identified with random biopsies, confirmation of dysplasia by a second gastrointestinal pathologist is advised, followed by referral of the patient to an endoscopist with expertise in IBD surveillance using chromoendoscopy and high-definition imaging.

Apart from dysplasia detection, the role of endoscopy is rapidly evolving for prediction of clinical outcome and relapse of IBD patients. In this context, modern image-enhanced endoscopy systems have already shown their potential and we are expecting the long-term results of ongoing studies within the upcoming 2 years.

Management of IBD patients is evolving toward personalized medicine with the aim of reducing side-effects, costs and greater effectiveness of treatment. In this context, early data have already shown the potential of molecular endoscopic imaging for prediction of therapeutic responses to anti-TNF antibody therapy. Although the safety of topical application and intravenous injection of fluorescence-labeled structures in human patients have already been described, it appears obvious that additional studies addressing the safety of molecular endoscopic imaging are needed. However, even taking into account the recent progress in the field of computer-assisted diagnosis, one could anticipate that prediction of therapeutic response based on molecular endoscopic imaging might soon become a valuable tool once the safety questions have been fully answered.

Taken together, the role of advanced endoscopic imaging in IBD is rapidly evolving (Table 1). Starting with surveillance and dysplasia detection many years ago, endoscopy today is evaluated more for prediction of clinically relevant outcome parameters and for guidance of pharmaceutical therapies.

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