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MINIREVIEWS

New endoscopic imaging techniques in surveillance of inflammatory bowel disease

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Abstract

Endoscopy plays a crucial role in the management of inflammatory bowel disease (IBD). Advances imaging techniques allow visualization of mucosal details, tissue characteristics and cellular alteration. In particular chromoendoscopy, magnification endoscopy, confocal laser endomicroscopy and endocytoscopy seem to have the possibility to radically modify the approach to surveillance and decision making. Dye-based chromoendoscopy (DBC) and magnification chromoendoscopy improve detection of dysplasia, and evaluation of inflammatory activity and extension of ulcerative colitis and are thus considered the standard of care. Dye-less chromoendoscopy could probably replace conventional DBC for surveillance. Narrow band imaging and i-scan have shown to improve activity and extent assessment in comparison to white-light endoscopy. Confocal laser endomicroscopy (CLE) can detect more dysplastic lesions in surveillance colonoscopy and predict neoplastic and inflammatory changes with high accuracy compared to histology. This technology is best used in conjunction with chromoendoscopy, narrow-band imaging, or autofluorescence because of its minute scanning area. This combination is useful for appropriate tissue classification of mucosal lesions already detected by standard or optically enhanced endoscopy. The best combination for IBD surveillance appear to be chromoendoscopy for identification of areas of suspicion, with further examination with CLE to detect intraepithelial neoplasia. However cost, availability, and experience are still an issue.

Key words: Ulcerative colitis; Crohn's disease; Endoscopy; Surveillance; Colorectal cancer

Core tip: Modern endoscopic imaging techniques might change the approach to surveillance of patients with inflammatory bowel disease (IBD). They allow visualization of mucosal details, tissue characteristic and cellular changes. In particular chromoendoscopy,

magnification endoscopy, confocal laser endomicroscopy and endocytoscopy promise to radically modify surveillance and decision making in IBD, however their widespread availability and cost/effectiveness is an issue.

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INTRODUCTION

Endoscopy plays a basic role in the diagnosis, management, prognosis and surveillance of inflammatory bowel diseases (IBD). IBD is a chronic lifelong condition that requires careful medical management and follow-up because it can be associated with significant morbidity, need for hospitalization and surgery. Once IBD is suspected based on clinical signs, symptoms, laboratory markers and/or radiology studies, endoscopy with mucosal biopsies is the gold standard to confirm the diagnosis. After diagnosis, endoscopic examination is important to assess the disease extent and severity, to monitor disease activity, to provide endoscopic treatment and for surveillance of dysplasia and neoplasia[1,2]. Patients with longstanding IBD have an increased risk of colorectal cancer (CRC) compared to the general population and the CRC risk appears to be the same in Crohn's colitis and ulcerative colitis (UC)[3,4]. The exact mechanism behind this increased risk are unknown, although data suggest a profound role of chronic inflammation of the intestinal mucosa[5]. There are several meta-analysis evaluating the incidence of CRC in IBD patients. Eaden *et al*[6] reported an overall prevalence of CRC in UC patients of 3.7%, Ekbom found a standardized incidence ratio (SIR) of 5.7 (95%CI: 4.6-7.0)[7] while Bernstein *et al*[8] reported a SIR of 2.3 (95%CI: 2.0-2.6) in UC patients and 2.6 (95%CI: 1.69-4.12) in CD patients. There are many risks factors implicated in the development of CRC: the duration of the inflammatory disease, the extension of the disease, the degree of inflammation, the coexistence of primary sclerosing cholangitis (PSC), and family history of CRC. The association between duration of the disease and development of CRC is the rationale for endoscopic surveillance, that should begin after 7-8 years of initial symptoms complain. The extent of colitis is another important risk factor of CRC risk[9]. CRC risk is high in patients with extensive colitis, intermediate in left-colitis and low in proctitis. Risk assessment of CRC also critically relies on endoscopic appearance of the severity of disease activity: both endoscopic and histological inflammations were shown to be associated with increased risk. The presence of post-inflammatory polyps probably reflects a previous severe inflammation and is associated with an increased risk of CRC development. On these bases, is clear how surveillance endoscopy permits detection of dysplasia and early detection of CRC, leading to an improvement of prognosis[10]. Surveillance should be performed in everyone with UC or Crohn's colitis, except patients with proctitis or Crohn's colitis affecting only one segment of colon. Regarding optimal surveillance intervals there is not clear evidence yet but individualizing intervals based on risk stratification is basic. Patients with an high risk factors for development of CRC should perform a colonscopy every one year (extensive colitis with severe inflammation, diagnosis of PSC, stricture and dysplasia identified in the last five years, history of CRC in a first-degree relative with less than 50 years). Patients with intermediate risk factors should perform a colonscopy every 2-3 years (extensive colitis with mild or moderate inflammation, presence of post-inflammatory polyps, history of CRC in a first degree relative at 50 years and over). For patients with a low risk of CRC, guidelines advise to perform a colonscopy every 5 years[6,7].

CRC mostly develop in raised protruded lesions but it can also occur in flat lesions or in mucosa with normal feature too. In the recent past, raised neoplastic lesions arising within an area of inflammation have been termed dysplasia-associated lesions/masses (DALMs)[11,12]. These lesions may present low or high dysplasia, *in situ* and invasive cancer. Subsequently the term adenoma-like mass (ALM) has been introduced to describe polyps with dysplasia in an area of colitis, but endoscopically very similar to sporadic adenomas[13]. However, no clear endoscopic, histologic or immunohistochemical difference between DALMs, ALMs and sporadic adenomas has been described, although some endoscopic lesions are more common in UC than non-UC patients. Therefore the terms DALM and ALM are more recently dismissed. Actually, lesion's morphology is best described by the standardized terminology of the Paris classification[14] either in abbreviated (0-Ⅱa) or extensive form (*e.g,* flat, minimally elevated lesion), although some irregular or less defined lesions may not be easily categorized. A detailed endoscopic description of morphology, pit pattern, and grade of background mucosal inflammation is requested. Moreover, current terms to describe low and high-grade dysplasia are also low grade non-invasive neoplasia or high grade non-invasive neoplasia, respectively[15]. Surveillance endoscopy white standard light endoscopy and multiple random biopsies may miss a quantum of lesion. Previous literature data showed that in up to 50% of colitis-associated neoplasms, the lesions were not visible at endoscopy[16]. This problem have suggested to perform an high number of random biopsies, every 10 cm of colon in four quadrants, which is a time consuming and costly approach, either for endoscopists and pathologists[17]. Recently,

new emerging endoscopic imaging techniques have been introduced thus allowing a better visualization of mucosal and submucosal lesions[18]. This review will focus on these endoscopic modalities, highlighting their potential role in the surveillance of IBD.

MAGNIFICATION

Magnification endoscopy is performed by an endoscope with a variable lense, which allows to modify the magnification degree until 150-fold. Thanks to this feature is possible to have a detailed characterization of the mucosal surface and the pit pattern. It has been shown that magnification endoscopy combined with chromoendoscopy has the potential to improve targeting biopsy examination in patients with long-standing colitis and facilitate early detection of intraepithelial neoplasia and colorectal cancer[19].

CHROMOENDOSCOPY

Chromoendoscopy uses different staining techniques and endoscopic/optical or computer-based colour programs to enhance the mucosal detail and submucosal vascular pattern; this procedure improve detection of mucosal lesions and permit a more precise characterization. Currently, chromoendoscopy is distinguished in dye-based (DBC) and dye-less imaging techniques (DLC).

Dye agents uses in DBC can be grouped in three types: Contrast agents (Indigo carmine and Acetic acid), Absorptive agents (Toluidine blue, Lugol, Cresyl violet and Methylene blue) and Reactive staining agents (Congo red and Phenol red). These agents are frequently used through spraying or catheters. Chromoendoscopy in combination with high magnification, allows a better definition of spreading and degree of inflammation, if compared with standard white light colonoscopy, in particular in patient with IBD. In addition, these techniques highly improve early detection of intraepithelial CRC[20].

A randomized controlled trial has evaluated the chromoendoscopy for early detection of intraepithelial neoplasia and CRC in UC. A total of 165 patients with long-standing UC were randomized at a 1:1 ratio to undergo conventional colonoscopy or colonoscopy with chromoendoscopy using 0.1% of methylene blue. In the chromoendoscopy group, there was a significantly better correlation between the endoscopic assessment of degree (P = 0.0002) and extent (89% *vs* 52%; P < 0.0001) of colonic inflammation and the histopathologic findings compared, with the conventional colonoscopy group. In addition, significantly more intraepithelial neoplasia were detected in the chromoendoscopy group (32 *vs* 10; P = 0.003). Therefore DBC showed a more accurate diagnosis of extent and grade of inflammatory in UC compared with standard white-light endoscopy and, more importantly, improved early identification of intraepithelial dysplasia and CRC in patients with UC[21]. Some other trials and a meta-analysis evaluated pancolonic chromoendoscopy for detection of dysplasia in UC. Two of these have demonstrated that biopsies guided by dye spray revealed more dysplasia than random biopsies (P = 0.02 and P = 0.001, respectively)[22,23]. A meta-analysis showed a diagnostic odds ratio of 17.5 with a pooled sensitivity of 83.3% and a specificity of 91.3%. Therefore, chromoendoscopy appear to have an high sensitivity with an high diagnostic accuracy for detection of dysplasia[24]. High-magnification chromo-colonoscopy is also a tool for reliable assessment of disease extent in compared to conventional colonoscopy[25]. However, dye-based chromoendoscopy has some potential limitations, mainly its availability but especially the length of procedure. Moreover, dyes do not always coat all surface required and this procedure does not allow a detailed analysis of sub-epithelial capillary network, which is another important feature in the diagnosis of CRC.

DLC is grouped in optical chromoendoscopy and virtual chromoendoscopy. Optical chromoendoscopy include narrow band imaging (NBI; Olympus®). Virtual chromoendoscopy include I-scan (Pentax®) and Fujinon intelligent colour enhancement (FICE; Fujinon®). NBI uses an optical filters, applied on the light source of endoscope, which narrow the bandwidth of spectral transmittance. This methodology highly enhance the visualization of blood vessels pattern. I-scan and FICE, instead, use digital post-processing with computed spectral estimation to achieve a better tissue contrast[26]. The latter are not dependent on the presence of optical filters inside of the video endoscope. FICE and i-scan use endoscopic images and reconstruct virtual images in realtime by increasing the intensity of blue light to a maximum and by decreasing red light and green light to a minimum resulting in an improved contrast of the capillary patterns and enhancement of the mucosal surface. A nice study of Matsumoto *et al*[27] evaluated magnifying colonoscopy with NBI for the diagnosis of intraepithelial neoplasia in ulcerative colitis. In this trial it was showed that the tortuous pattern determined by NBI colonoscopy could be a clue for the diagnosis of dysplasia during surveillance for UC. Van den Broek *et al*[28] undertaken a randomized trial to compare NBI and high definition white-light colonoscopy (HDE). Twenty-five patients with UC underwent NBI or HDE in a random order with at least 3 wk of interval between the two endoscopies. The study showed that NBI does not improve the detection of neoplasia in patients with UC compared to HDE endoscopy. In addition, NBI was insufficient in differentiating neoplastic from non-neoplastic mucosa[28]. Subsequently, Van den Broek *et al*[29], have tested the efficacy of trimodal imaging for the surveillance of

neoplasia in fifty patients with longstanding UC. In the trial, each segment of colon was inspected twice, once with autofluorescence imaging (AFI) and once with standard white light endoscopy, in a randomized order. This study showed that AFI decreased the necessity of random biopsies improving the detection of neoplasia. In addition, NBI pit pattern analysis predicted the histologic findings with a moderate accuracy while AFI colour appeared useful in excluding the presence of neoplasia[29]. In another prospective, randomized study, NBI was compared with CE for the detection of intraepithelial lesions. NBI was less time consuming and equally effective compared to chromoendoscopy for identification of intraepithelial neoplasia (26.9 ± 9.9 min *vs* 15.7 ± 5.6 min, $P < 0.01$). NBI resulted in a significantly lower false-positive biopsy rate and a similar true-positive rate ($P = 0.001$). The percentage of missed intraepithelial neoplasia lesions was superior with NBI, although not reaching statistical significance. However, given the intraepithelial neoplasia miss rate, NBI should not be recommended as the gold standard endoscopic technique for surveillance in IBD[30]. Only one trial tested FICE in a IBD setting, the latter showed that FICE does not improve detection of ulcers and erosions due to Crohn's disease, but this data should be evaluated in larger prospective trials[31]. Finally a study tested the efficacy of high definition (HD) endoscopy compared to i-scan or chromoendoscopy with methylene blue (0.1%) in screening for colorectal cancer and it was found that both i-scan and chromoendoscopy identified more lesions compared to high definition endoscopy alone[12,32].

Given these evidences, ECCO consensus guidelines on endoscopy in IBD recommend pan-colonic methylene blue or indigo carmine chromoendoscopy during surveillance colonoscopy, with targeted biopsies of any visible lesion. When chromoendoscopy is not available multiple random biopsies should be performed.

CONFOCAL LASER ENDOMICROSCOPY

Confocal laser endomicroscopy (CLE) has been first introduced in 2004. It can be performed with two devices: one integrated into endoscope (e-CLE; Pentax®, Tokio, Japan), and one using a mini-probe through the scope (p-CLE; Cellvizio, Mauna Kea Technologies, Paris, France). Confocal laser microscopy consists of focusing a laser ray onto the mucosal surface and filtering the returned light by means of a small pinhole which rejects out of focus light. The illumination and detection systems are in the same focal plane and are termed confocal. After passing the pinhole, the fluorescent light is detected by a photo-detection, transforming the light signal into an electrical one, that is recorded by a computer. All detected signals from the illuminated spot are captured and measured. As the laser scans over the plane of interest, a whole image is obtained pixel-by-pixel and line-by-line, whereas the brightness of a resulting image pixel corresponds to the relative intensity of detected fluorescent light. The gray-scale image created is an optical section representing one focal plane within the examined specimen. Real-time confocal laser scanning microscopy-sequences (1 min-duration) are recorded and stored digitally for later evaluation. CLE evaluation and its high-quality images have shown high agreement with the histology[33-35]. A number of studies have investigated the usefulness of CLE in the diagnostic work-up of IBD, especially in ulcerative colitis. CLE has shown that could have a role in assessing the extension and the activity of disease. Moreover it could be useful in targeting biopsies and to improve the early detection of dysplasia. The most recurrent histologic modification in crypt architecture of UC are the crypt dilation, disorganized arrangement of crypts, dilatated spaces between crypts, destruction or fusion of crypts and crypt abscess. The microvascular modifications often consist of dilatation and swelling of branching vessels. Dysplasia is identified by darks cells with depletion of mucin and density reduction of goblet cell. The architectural pattern is often disorganized, epithelial thickness is variable with dark epithelial border and villiform structures. The blood vessels are enlarged with anomalous branching and weak orientation to basement membrane. The Miami classification system has been designed, with a worldwide consensus, for p-CLE images[36]. Due to the technical differences, p-CLE images are not comparable to e-CLE images and there is not a worldwide accepted classification f CLE images in UC, so this is a limitation of this technique[37]. Watanabe *et al*[38] and Li *et al*[39] reported on inflammation activity assessment by CLE. The inflammation activity assessment includes crypt architecture, cellular infiltration, and vessel architecture. These studies showed that images obtained with CLE techniques provided information that are similar to conventional histology, with a good differentiation between active and non-active UC during endoscopy examination. In a double-blind trial, CLE was shown to be superior to NBI[40]. In another study evaluating more than one hundred polyps, probe-based CLE showed a trend of higher sensitivity compared to NBI (86% *vs* 64%, $P = 0.08$), with similar accuracy (82% *vs* 79%, $P = 0.59$). The overall accuracy of using probe-based CLE together with NBI to predict polyp histology was greater than 94%[41]. In the management of patients with UC, an important diagnostic goal, is the detection of dysplasia/neoplasia, with a small number of biopsies, thus minimizing time and cost. In this contest Kiesslich *et al*[42] have shown that identification and diagnosis of dysplasia in UC could be maximized by using together pan-chromoendoscopy and targeted CLE, achieving high value of diagnostic accuracy (sensitivity 94%, specificity 98%). Subsequently this result has been confirmed also by Van den Broek *et al*[43]. A trial of longstanding ulcerative colitis, exploring

the efficacy of the combined application of CE and targeted p-CLE in diagnosing dysplasia, has underlined the high diagnostic accuracy of such procedures compared to standard histology (sensitivity 100%, specificity 90%, positive predictive value 83%, and negative predictive value 100%)[44]. Another recent study prospectively evaluated the clinical applicability and predictive power of endomicroscopy for the *in vivo* differentiation of dysplasia-associated lesional mass (DALM) or adenoma-like mass (ALM). This trial showed that the accuracy of endomicroscopy was 97% with an excellent agreement between endomicroscopy and histopathological diagnosis[45]. Neumann *et al*[46] have explored the clinical utility of CLE also in patients affected by Crohn's disease (CD), determining whether the disease activity can be graded by using CLE. The authors proposed a CLE score for assessing CD activity *in vivo*, with a potential utility of predicting the CD course and response to medical therapy. CLE application in IBD has been evaluated also under a prognostic view. A trial has shown that cell shedding and barrier loss detected by CLE are able to predict relapse of IBD and therefore has a potential role as diagnostic tool for the management. The sensitivity, specificity and accuracy for the CLE grading system to predict a flare were 62.5%, 91.2% and 79%, respectively[47]. A second paper confirmed the prognostic power of CLE in predicting the course for other relevant clinical end-points for patients affected by IBD, such as future hospitalization or surgery[48]. No data are available to compare p-CLE with e-CLE. pCLE has some advantages and disadvantages compared with eCLE. Advantages include the greater versatility of pCLE probes, which can be used in conjunction with virtually any endoscope (high-resolution endoscopes, NBI, cholangioscope, *etc.*), and acquisition at video frame rate of 12 frames/s, allowing *in vivo* imaging of capillary flow. Disadvantages include a slightly lower resolution (approximately1 μm compared with 0.7 μm for eCLE) and smaller field of view (240 μm *vs* 600 μm).This technology is best used in conjunction with chromoendoscopy, narrow-band imaging, or autofluorescence because of its minute scanning area. So it is useful only for appropriate classification of tissue at a mucosal site already detected by standard or optically enhanced endoscopy. The best combination in IBD surveillance appears to be chromoendoscopy for identification of areas of suspicion, and that examination with CLE to confirm intraepithelial neoplasia. However, confocal techniques are limited by high costs and need of contras media, such as intravenous Fluorescein. In addition, more prolonged time for the procedure is inevitable and the operator's expertise and learning curve is an issue. Larger studies on the combined use of such modalities are required to assess cost/effectiveness.

ENDOCYTOSCOPY

Endocytoscopy (EC; Olympus®) is a new imaging technique, enabling microscopic imaging of the mucosal layer of the gut at a magnification up to 1400-fold. Endocytoscopy is based on a contact light microscope which enables real-time visualization of cellular structures of the superficial epithelial layer in a plane parallel to the mucosal surface. Systems integrated into the distal tip of an endoscope (iEC) and probe-based (pEC) are available. Probe-based systems consist of handheld miniprobes, inserted through the accessory channel of a standard endoscope. The device provides ultra-high magnification imaging from an optical sampling site of about 0.5 mm in diameter. Endocytoscopy requires preparation of the mucosal layer with absorptive contrast agents like methylene blue or toluidine blue[13]. The technique seems to be useful and safe for the examination of gastrointestinal mucosal surfaces[49], and could recognize neoplasia in aberrant crypt foci and distinguish cancerous lesions from non-cancerous ones[50]. A trial has recently showed the value of EC for assessment of inflammatory disease activity and differentiation of single inflammatory cells in patients with IBD. In that study concordance between EC and histopathology for grading intestinal disease activity in CD was 100%[51].

CONCLUSION

The endoscopy is crucial for diagnosis, prognosis, and management of IBD. In addition, a critical role is that of surveillance of colorectal cancer and detection of dysplasia. In this context the colonoscopy is traditionally coupled with histology, with the need of multiple biopsies. This is suboptimal for dysplasia detection and time consuming for either endoscopists and pathologists. The utilization of chromoendoscopy, possibly combined with magnification, is actually considered the "gold standard", given the adequate diffusion of the methodology and the opportunity to perform targeted rather than random biopsies. In contrast, so far, the techniques of so called virtual or optical chromoendoscopy, although more operator friendly, have not proven to be comparable to chromoendoscopy with vital colorants. However, technology is on progress and several comparative trials underway. Finally, future development and diffusion of confocal endomicroscopy or endocytoscopy could prove further advantage including the need of less biopsies or avoid histology. However, possible medico-legal consequences should be taken into account, and cost/effectiveness, learning curve and length of procedure should be taken into account.

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