Leading article

The role of endoscopy in inflammatory bowel disease

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Inflammatory bowel disease (IBD) is a group of chronic immune-mediated disorders of the gastrointestinal tract. It is often the result of the interaction of genetic and environmental factors. The role of endoscopy in disease surveillance is unprecedented. However, there is considerable debate in therapeutic goals in IBD patients, ranging from the resolution of clinical symptoms to mucosal healing. Furthermore, deep remission has recently been advocated for altering disease course in these patients. Additionally, neoplasia continues to be a significant cause of morbidity and mortality in IBD patients. This review discussed the role of several endoscopic techniques in assessing mucosal healing and neoplasia with emphasis on novel non-invasive endoscopic techniques.

KEY WORDS: endoscopy, inflammatory bowel disease, mucosal healing, neoplasia.

INTRODUCTION

Inflammatory bowel disease (IBD) is a group of immune-mediated chronic inflammatory disorders of the small and large intestines.1 It is often the result of the interactions between genetic factors and environmental conditions. Ulcerative colitis (UC) and Crohn’s disease (CD) are the two clearly distinct pathophysiological entities of IBD. The incidence of UC is approximately 1.2–20.3 cases per 100 000 persons per year, compared to 0.03–15.6 cases per 100 000 persons per year in CD.2 Approximately 1.4 million North Americans are diagnosed with some variant of IBD each year.3 Although UC and CD are distinct disease processes, there is much overlap of symptomatology resulting in significant dilemma in their diagnosis and management amongst physicians. Typically, UC is characterized by continuous disease involvement of the superficial mucosa of the colon proximally from the anus.4 On the contrary, CD is a patchy inflammatory disease that often involves the small intestine, but can spread from the mouth to the anus.5 However, small intestinal involvement is not a specific feature of CD as up to 10% of patients with UC may experience “backwash ileitis”.6,7 This necessitates the need for extensive biopsies and histological analysis when considering a diagnosis of IBD. Despite this, approximately 15% of the patients with undifferentiated symptoms of IBD are classified as IBD unclassified (IBDU).8 A diagnosis of IBDU results in poorer prognosis and worse quality of life (QoL) in such patients.9

Chronic inflammation as a result of IBD can lead to significant consequences. Once a diagnosis of IBD is confirmed, patients require close follow-up to avoid potentially fatal outcomes of their primary disease process. Perhaps the grimmest consequence is the development of neoplasia.10,11 First described in 1925 by Dr. Crohn, colorectal cancer (CRC) secondary to IBD accounts for significant disease burden and
mortality. Furthermore, since histological inflammation is a significant risk factor for neoplasia in UC, the role of endoscopy in regular neoplastic surveillance is highly unprecedented. Techniques such as colonoscopy with ileoscopy, narrow band imaging (NBI), chromoendoscopy (CE), confocal laser endomicroscopy (CLE) and fluorescence endoscopy (FE) are available for disease surveillance.

In addition to the regular neoplastic surveillance, active disease surveillance via endoscopy is critical in ensuring adequate QoL, decreasing rates of hospitalizations and improving overall survival. In fact, the presence of endoscopic lesions such as severe colonic ulcerations has been found to be associated with an increased risk of colectomy and overall mortality. The concept of mucosal healing (MH) was introduced as a primary endoscopic end-point for predicting disease outcomes in patients with established IBD. Several endoscopic techniques such as small bowel capsule endoscopy (SBCE) and endoscopic ultrasound (EUS) have been investigated in their ability to detect MH and monitor disease activity in patients on therapies for established IBD.

In this review, we described the important role of endoscopy in neoplastic surveillance in patients with established IBD, with a particular emphasis on novel non-invasive endoscopic techniques. Furthermore, we described the effect of MH on the progression of disease activity as well as the roles of several endoscopic techniques in assessing mucosal activity. Finally, we briefly reviewed the role of endoscopy in postoperative disease surveillance of IBD patients. As we learn more of the chronicity of IBD and impact on daily QoL, it is inevitable that newer non-invasive endoscopic techniques will be implemented to improve survival and to decrease the overall risks of serious complications.

ENDOscopy IN NEOPlastic SURveillance OF IBD PATIENTS

Neoplasia continues to remain a significant burden in patients with IBD. Traditionally, the risk of CRC has been significant in patients with UC compared with those with CD. It has been estimated that the risk of developing CRC is approximately 3.7% in patients with UC, with CRC causing death in 15% of those patients. In patients with CD, the relative risk of developing CRC is 23.8% in patients having severe colitis, with a cumulative risk of 23% after 40 years of diagnosis. The risk factors for developing CRC have been extensively examined, including a disease duration of longer than 10 years, the presence of left-sided colitis, terminal ileitis, pancolitis and severe inflammation. Additionally, the presence of primary sclerosing cholangitis has been shown to increase the risk of developing CRC (Table 1).

Due to a significant risk of neoplasia, the most important use of “real-time” endoscopy in IBD may be efficient and accurate to identify dysplastic or neoplastic tissues to reduce the morbidity and mortality. Current guidelines for neoplastic surveillance are similar in patients with UC and CD, suggesting the use of annual conventional white-light colonoscopy after 8–10 years of extensive and severe UC. For left-sided colitis, it is recommended that screening commences annually after 15 years of diagnosis. Surveillance colonoscopy is also recommended in patients with disease remission. Furthermore, it is recommended by the American Society for Gastrointestinal Endoscopy (ASGE) that up to four random biopsies be obtained every 10 cm of colonic tissues with additional sampling at the endoscopist’s discretion. However, in patients with known pancolitis, endoscopists are often required to obtain more than 50 biopsies, which is a costly and highly ineffective feat. Despite these guidelines, to our knowledge, there have been no controlled studies showing a decrease in mortality from colonoscopic neoplastic surveillance in patients with IBD. Additionally, there have been several case series as well as a Cochrane analysis, demonstrating no evidence of improved survival from periodic colonoscopic screening.

Approximately 50–80% of neoplastic lesions are missed by regular screening pancolonoscopy. Several factors such as the inability for pancolonoscopy to detect neoplasia in normal-appearing mucosa (flat lesions) and the inability to determine the severity of mucosal inflammation by endoscopy alone contribute to this phenomenon.

Table 1. Risk factors for developing neoplasia in patients with inflammatory bowel disease (IBD)

| Risk Factor                                      |
|-------------------------------------------------|
| Inflammation >10 years                          |
| Post-inflammatory polyps or strictures          |
| Left-sided colitis                              |
| Terminal ileitis                                |
| Pancolitis                                      |
| Severe inflammation                             |
| Primary sclerosing cholangitis                   |
| Family history of CRC (first-degree relatives)  |
| Smoking history in CD                           |
| Earlier age at diagnosis of IBD                  |

CD, Crohn’s disease; CRC, colorectal cancer.
colonoscopy in detecting dysplastic lesions earlier to avoid the progression to neoplasia.

NBI is a technique of virtual CE that employs selective light filters to produce processed images of vascular structures. It was thought that NBI would be able to reduce the need for numerous biopsies as well as to reduce the costs associated with the current surveillance guidelines. However, initial studies demonstrated no difference between this procedure and conventional colonoscopy in the detection rates of dysplasia and costs. NBI has also been considered equivalent to CE for detecting intraepithelial neoplasia with an advantage of decreased procedural time. However, it is not recommended as a first-line procedure due to a high miss rate of dysplastic lesions.

CE relies on targeted biopsies using methylene blue or indigo carmine dye-spray to improve the sensitivity during colonoscopic surveillance. In this technique, the dye is sprayed through a catheter via the working channel of the colonoscope. Once applied, methylene blue is absorbed by non-inflamed mucosa whereas inflamed mucosa is spared. Indigo carmine dye stains dysplastic tissues and spares non-inflamed mucosa. In patients with UC, early studies by Kiesslich and colleagues reported a statistically significant increase in the detection rates of intraepithelial neoplasia and CRC using CE. Similarly, Marion and colleagues demonstrated that targeted biopsies with methylene blue dye spray in 115 patients with either UC or CD revealed significantly more dysplasia and neoplasia than standard white-light endoscopy. Several other studies have reported an increased diagnostic yield for the detection of neoplasia using CE compared with conventional colonoscopy with a reduced number of biopsies. A recent meta-analysis of six studies including 1277 patients concluded CE to be significantly more effective than conventional white-light colonoscopy for detecting dysplasia in IBD patients. However, the disadvantages of CE include the requirement of careful cleaning of the entire colon prior to spray application to prevent unequal spread of dye, the cost of procedure, and safety concerns with the use of methylene blue. Some experts have suggested that methylene blue may cause mutagenic effects on DNA and result in further abnormalities of normal colonic tissues. However, no direct correlation has demonstrated this effect. As such, the ASGE and the Crohn’s and Colitis Foundation of America Colon Cancer in IBD study group endorse targeted biopsies using CE performed only by experienced endoscopists as a suitable alternative to the traditional colonoscopy.

A low-power laser and fluorescent agents such as cresyl violet and acrilavine hydrochloride are used for CE illumination of the mucosa. Integrated into the tip of a conventional endoscope or passed through the working channel, a miniature microscope allows histological evaluation of intestinal and colonic tissues in a “real-time” manner. Crypt and vascular architecture abnormalities may appear during CE indicating the areas of concern and potentially immediate diagnosis of dysplasia or intraepithelial neoplasia. Hence, CE allows targeted biopsies as well as accurate diagnosis of abnormal tissue patterns. Interestingly, to detect dysplasia with as minimal biopsies as possible, CE has been studied extensively in combination with CE, termed chromoscopy-guided endomicroscopy. By pre-staining the mucosa with CE, endomicroscopy can then further characterize suspicious lesions by in vivo histology. Specifically, these dyes allow for the accentuation of surface patterns and stain pit patterns in the colon. Kudo et al. developed this pit pattern classification that may be applied during CE and CLE combination endoscopies to classify mucosal changes into 5 categories, varying from non-neoplastic changes to invasive carcinoma.

By applying this method, Kiesslich et al. were able to demonstrate a 4.75-fold increase in the detection rate of neoplasia compared to white-light colonoscopy, whereas reducing biopsy specimens by 50%. Furthermore, studies have shown that confocal chromoscopic endomicroscopy is superior to CE alone. Rispo and colleagues demonstrated the sensitivity and specificity of CLE for detecting dysplasia to be 100% and 90%, respectively, with the targeted CE/CLE combination maximizing diagnostic accuracy. Hence, some experts have suggested that random biopsy guidelines should be replaced by CLE/CE combination-targeted biopsy protocols. Drawbacks of this approach include high costs, requirements of advanced training for endoscopists and the inability of the endomicroscope to probe beyond superficial mucosal layers. Despite this, the combination of CLE and CE offers great promise in reducing the number of biopsies needed and improving the detection rates of dysplasia and eventually CRC at earlier and potentially curable stages.

Other innovations in neoplasia surveillance include FE. FE relies on the selective conversion of 5-aminolevulinic acid (5-ALA) to fluorescent protoporphyrin IX by neoplastic tissues. Topical administration with 5-ALA allows neoplastic tissues to be stained
with a reddish hue upon illumination with blue monochromatic light during conventional endoscopy. Messmann and colleagues were the first to apply this technique in UC and revealed a sensitivity of 87–100% in detecting dysplastic lesions. Unfortunately, Ochsenkühn and colleagues evaluated a total of 688 biopsies and concluded a low yield of correlation between the areas of dysplasia and red fluorescent stain. Hence, future prospective controlled trials evaluating the use of fluorescent endoscopy in detecting dysplasia are needed for it to be recommended as a first-line tool for neoplastic surveillance.

ENDOSCOPY IN DISEASE SURVEILLANCE IN ESTABLISHED IBD

In patients with established IBD, endoscopic surveillance of disease activity is also important in establishing the severity of disease, assessing response to therapies and diagnosing complications such as strictures and fistulas. Over the last several decades and with the advent of novel pharmacological agents such as antibodies to tumor necrosis factor (TNF), there has been a shift in long-term treatment goals. The traditional corticosteroids (CS) as well as immunomodulators (IMD) such as methotrexate and azathioprine (AZA) were considered first-line therapies for IBD. However, despite their abilities to improve the patient's symptoms, these medications are unable to consistently induce MH. Furthermore, the proportion of patients achieving MH varied from 0% to 73% in CD patients treated with CS and IMD. AZA was also superior to CS such as budesonide in inducing MH. Similarly, in patients with UC, 5-aminosalicylic acid (5-ASA) and its derivatives such as balsalazide and mesalazine induce MH in a wide range of patients (16–78%), with MMX® Mesalazine being the most effective. The novel disease modifying agents such as anti-TNF agents were the first to consistently induce MH in patients with active IBD. In the ACCENT 1 trial, MH was shown in CD patients treated with infliximab (IFX). In UC, IFX had induced MH in 62.0% of patients by week 8 of treatment and 50.4% by week 30. Similarly, adalimumab is also effective in inducing MH in IBD patients with fewer relapse rates and hospitalizations. Hence, the inability to achieve MH has emerged as a significant predictor of mortality and morbidity in IBD patients and shifted the focus of target for novel pharmacological agents.

In 2007, the International Organization of IBD (IOIBD) defined MH as an absence of erosions, ulcerations, friability and bleeding within gut mucosa. The importance of mucosal ulceration in predicting MH derives from studies demonstrating that ulceration of greater than 10% of mucosal surface increased the risk of future colectomy. Despite the IOIBD recommendations, several studies do not include erythema and friability as the predictors of failed MH. Unfortunately, there is no validated definition of MH in IBD with great variability in definitions amongst clinical trials and research studies. Hence, there is a need for universally validated definition of MH.

Despite this, MH remains a primary end-point in a number of clinical trials, as it is associated with improved QoL and reduced rates of hospitalizations. It may be more applicable for the investigation of MH in patients with UC rather than in those with CD due to superficial mucosal involvement in UC. In patients with UC, the achievement of MH has been associated with reduced doses of CS use and decreased risk of colectomy. In the “Step Up versus Top Down Study”, patients with complete MH had a higher probability of clinical remission without the requirement of long-term use of CS. Furthermore, patients with UC and endoscopically confirmed MH had a similar risk of developing CRC to the general population. While in patients with CD, there is limited data. A few studies have reported that the presence of extensive mucosal ulceration in active CD patients increased significantly the risk of future colectomy. One Norwegian study demonstrated decreased surgical rates in CD patients with MH at one-year follow-up. Similarly, only 11% of CD patients with MH required surgery at 5-year follow-up. Therefore, the role of endoscopy in assessing MH is critical in preventing further morbidity from the primary disease process. Traditionally, ileocolonoscopy has been considered the first-line investigation in assessing disease severity of IBD. However, ileocolonoscopies are invasive and do not have the ability to analyze deeper layers of intestinal mucosa. Therefore, other modalities have been introduced to monitor and assess the presence of MH in IBD patients.

SBCE has been implemented in regular IBD surveillance and the assessment of the effects of medical management. Several studies have analyzed SBCE in detecting endoscopic lesions such as aphthous ulcers and large ulcers and eventually evaluating MH. A prospective study of 40 patients with active CD evaluated three findings, that is, the number of large ulcers, aphthous ulcers and length of time these lesions were visible. In patients treated with a combination of CS and biological agents, SBCE was able to...
detect the improvements in all three of those variables. More recently, in a retrospective study including 187 CD patients, the use of SBCE in assessing MH resulted in 52.3% of those undergoing changes in their medications.102 SBCE was also effective in distinguishing mild to moderate and severe inflammation. The complication rate was approximately 2.1%, the most common being capsule retention. Hence, the authors suggested the consideration of SBCE in established CD patients for disease surveillance. The importance of SBCE in assessing the effect of medical management of established IBD patients was also reported in several studies.102–107 Flamant et al. reported that the presence of jejunal lesions detected by SBCE was significantly correlated with a risk of disease relapse in two years.106 Additionally, Cotter et al. recently described the application of the Lewis score detected by SBCE for reporting small-bowel inflammatory activity. In patients with isolated small intestinal CD, the Lewis score should be used to assess therapeutic mucosal response as well as the complications of IBD such as strictures and ulcerations.108

EUS is a relatively novel technique introduced for the diagnosis and follow-up of IBD patients.109–111 Total colonic wall thickness as well as the presence of paracolic lymph nodes can be assessed by EUS in various anatomical regions around the colon except rectum.24,112 Additionally, EUS has a sensitivity of 97% in detecting inflammation in the sigmoid and descending colon. A prospective study evaluated the role of EUS in assessing disease activity in IBD patients to the treatment of CS.113 Although 79% of those patients achieved clinical symptomatic relief, only 34% had complete MH as assessed by EUS. Moderate to severe EUS scores at 3 months were associated with higher rate of mucosal inflammation at 15 months.113 Despite these advancements, the use of EUS is limited mainly to perianal disease. The accuracy of EUS to detect perianal fistulas secondary to IBD has been around 91%, which is similar to that of magnetic resonance imaging (MRI).114 Furthermore, EUS was able to detect the closure of perianal fistulas secondary to the treatment with IFX and 6-mercaptopurine. Additionally, EUS could be used to monitor the recurrence of fistula in patients with CD.115

Although MH is a primary end-point in many clinical trials, there are several uncertainties associated with this phenomenon. Firstly, the extent of MH required in improving clinical symptoms and survival is unknown. Investigators have found no difference in risk of colectomy between patients who achieved complete MH and those had partial MH.90 Furthermore, there is no information on when MH should be assessed in the disease course and after what duration of medical treatment is surveillance required. Additionally, there is concern that MH may be a highly subjective variable and have significant inter-endoscopist variance.116,117 This concern resonates from studies which have suggested that a significant number of patients develop clinical symptoms despite endoscopic presence of MH.118 Therefore, combining histological analysis at time of endoscopy may improve the sensitivity of MH detection.116 An important histological parameter that has been proposed in assessing MH is basal plasmacytosis, which has been associated with shorter relapse rates in patients with IBD.119 Basal plasmacytosis is defined as plasma cell infiltration within the deeper layers of lamina propria.120 The presence of basal plasmacytosis has the ability to predict clinical outcomes in patients with UC and may alter the definition of MH in future clinical studies.118

ENDOSCOPY IN POST-SURGICAL IBD PATIENTS

It has been estimated that up to 33% of patients with UC will eventually require surgery for a multitude of reasons such as neoplastic complications, pharmacological refractoriness and emergent conditions such as fulminant colitis.121,122 In patients with UC, surgery is thought to cure patients from their disease process. In a study of 390 UC patients who underwent restorative proctocolectomy with ileal pouch–anal anastomoses (IPAA), 94% achieved successful outcomes at 5-year follow-up.123 As such, IPAA is the surgical treatment of choice in patients with refractory UC.32 Further advantages of this surgery are retained anal sphincter function and a lack of chronic ileostomy.32 Several endoscopic modalities have been implemented in the postoperative surveillance and management of surgical complications after IPAA such as pouchitis, pouch dysplasia, pouch sinus and disease recurrence.

The most common complication of IPAA is pouchitis defined as the inflammation of the pouch mucosal surface.32,124 The reported cumulative risk of developing pouchitis is up to 50% in UC patients following IPAA with the greatest risk at 10 years after surgery.125–127 Symptoms of acute pouchitis such as abdominal pain, diarrhea and hematochezia significantly decrease the QoL and pose as a significant inconvenience for patients. Hence, surveillance for this complication is critical via the combination of endoscopy and histology.128 A recent study by Trovato et al. assessed the application of CLE and
standard white-light colonoscopy in diagnosing pouchitis in 18 patients after restorative proctocolectomy with IPAA.\(^\text{125}\) Features such as villous atrophy, mucosal inflammation and ulceration were analyzed by endomicroscopy. Using standard colonoscopy, only 39% of patients had visible signs of pouchitis. However, by CLE, the characteristics of pouchitis were discovered in up to 89% of patients, indicating a higher sensitivity for detecting mucosal changes. In addition to CLE, the role of SBCE in detecting pouchitis after IPAA has also been investigated.\(^\text{130}\) Calabrese et al. performed a single-blind, prospective cohort study in 15 patients with confirmed chronic pouchitis.\(^\text{130}\) All these patients also showed diffuse small intestinal lesions such as erosions and ulcerations on wireless SBCE. Despite promising data on SBCE and CLE, the ASGE guidelines suggest the use of standard white-light endoscopy in the surveillance for pouchitis due to small sample sizes as well as inconclusive evidence from the aforementioned studies.\(^\text{32}\)

CD patients often undergo ileocolonic resection for severe medically refractory disease affecting QoL. However, unlike curative surgery for UC, resection of refractory disease in CD does not offer a guaranteed cure for patients. In fact, it has been estimated that up to 30% of patients will have clinical recurrence of CD proximal to the surgical anastomosis and up to 90% will experience some degree of endoscopic recurrence at one-year follow-up.\(^\text{32,131,132}\) As such, the current gold standard for postoperative disease surveillance is ileocolonoscopy at 6–12 months after resection. However, due to reconstructed anatomy and the difficulty to intubate the neoterminal ileum, other endoscopic methods have been introduced. Bourrel and colleagues prospectively studied the role of SBCE vs that of ileocolonoscopy in 32 patients 6 months after ileocolonic resection.\(^\text{133}\) The sensitivity and specificity of SBCE were up to 76% and 100%, respectively, which were similar to those of ileocolonoscopy. The authors reported that SBCE was able to detect disease recurrence in anatomical regions that were unable to be intubated by ileocolonoscopy. Similarly, Pons Beltrán et al. demonstrated that SBCE had an improved ability of detecting disease recurrence compared to ileocolonoscopy.\(^\text{134}\) Therefore, there is promising data of alternative non-invasive endoscopic techniques for the surveillance of disease recurrence in IBD patients after surgery.

**SUMMARY AND FUTURE RESEARCH AVENUES**

The importance of achieving disease remission in IBD is unprecedented and requires the work of a well-organized multidisciplinary team. MH has emerged as a primary tool to assess disease activity and modify therapeutic regimens. However, there is controversy on the degree of healing required and the subjective nature of assessment between endoscopists. Recently, the concept of deep remission has emerged as perhaps the only way to improve symptoms and alter disease progression. Deep remission defined as lack of clinical, endoscopic and biochemical evidence of disease activity may improve the QoL and reduce hospitalization greater than achieving just MH. It remains to be shown whether deep remission will be implemented in future clinical trials as a primary end-point for assessing disease activity.

The role of endoscopy in neoplasia is critical in preventing morbidity and mortality. Newer modalities such as FE and CE offer the advantages of fewer biopsies and potentially reduced costs. Larger clinical trials are required in order to better delineate surveillance guidelines and endoscopic techniques. As we better understand the importance of endoscopy and specific features of each endoscopic technique, it is inevitable that perhaps a combination of endoscopic techniques such as CE/CLE will be required for early diagnosis of dysplasia. Regardless, there is ample data to suggest the benefit of newer non-invasive techniques in significantly improving QoL.

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