



REVIEW

Role of endoscopy in inflammatory bowel disease

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Abstract

Crohn's disease (CD) and ulcerative colitis (UC) constitute the two most common phenotypes of inflammatory bowel disease (IBD). Ileocolonoscopy with biopsy has been considered the gold standard for the diagnosis of IBD. Differential diagnosis of CD and UC is important, as their medical and surgical treatment modalities and prognoses can be different. However, approximately 15% of patients with IBD are misdiagnosed as IBD unclassified due to the lack of diagnostic certainty of CD or UC. Recently, there has been increased recognition of the role of the therapeutic endoscopist in the field of IBD. Newer imaging techniques have been developed to aid in the differentiation of UC vs CD. Furthermore, endoscopic balloon dilation and stenting have become an integral part of the therapeutic armamentarium of CD stricture management. Endoscopic ultrasound has been recognized as being more accurate than magnetic resonance imaging in detecting perianal fistulae in patients with CD. Additionally, chromoendoscopy may help to detect dysplasia earlier compared with white-light colonoscopy. Hence, interventional endoscopy has become a cornerstone in the diagnosis, treatment and management of IBD complications. The role of endoscopy in the field of IBD has significantly evolved in recent years from small-bowel imaging to endoscopic balloon dilation and use of chromoendoscopy in dysplasia surveillance. In this review article, we discuss the current evidence on interventional endoscopy in the diagnosis, treatment and management of IBD complications.

Key words: Inflammatory bowel disease; small-bowel imaging; therapeutic endoscopy; chromoendoscopy; endoscopic balloon dilation

Introduction

Inflammatory bowel disease (IBD) is characterized by chronic relapsing and remitting inflammation of the gastrointestinal (GI) tract. It is associated with significant morbidity and mortality, including frequent emergency-room visits, hospitalizations and surgery [1–3]. The overall incidence of IBD is approximately 29.6 per 100 000 [2]. The two most common phenotypes of IBD are Crohn's disease (CD) and ulcerative colitis (UC), which are

diagnosed based on clinical, endoscopic, histological, laboratory and radiological features. However, about 15% of patients with IBD cannot be classified into either CD or UC, and therefore are diagnosed as IBD unclassified (IBDU) due to lack of diagnostic certainty for CD or UC [4–6]. It is believed that these patients may have a slightly worse prognosis than classic UC [6].

The symptomatology of IBD varies, usually including abdominal pain or cramps, bloody diarrhea, urgency and tenesmus [7]. A significant number of patients also experience

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extra-intestinal manifestations such as erythema nodosum, pyoderma gangrenosum, oral lesions, scleritis, uveitis and sacroiliitis, and ankylosing spondylitis [8]. Furthermore, due to the transmural inflammatory nature of CD, patients can experience stricture at the terminal ileum, ileocecal valve or anastomosis [9]. Intestinal strictures from CD can result in obstructive complications, fistula, abscess and malnutrition [9, 10]. In addition, IBD patients have an increased risk for colorectal cancer. It is estimated that the risk of colon cancer for people with IBD increases by 0.5–1.0% yearly, 8–10 years after diagnosis [11]. IBD is a life-long diagnosis, with possible detrimental outcome. Therefore, it is important to make a correct diagnosis and differential diagnosis early in the disease process in order to efficiently control downstream complications.

Endoscopy plays a role in the diagnosis and management of IBD. For diagnosis, ileocolonoscopy has traditionally been considered the standard of care, but is limited due to accessing the colon and terminal ileum [12, 13]. Newer techniques such as video capsule endoscopy (VCE), confocal laser endomicroscopy (CLE) and deep small-bowel device-assisted enteroscopy (DBSE) have emerged as endoscopic techniques to differentiate the subtypes of IBD [14–16]. Furthermore, therapeutic endoscopy such as endoscopic balloon dilatation offers significant promise over traditionally used invasive procedures such as stricturoplasty and surgery in patients with the fibrostenotic phenotype of CD [17, 18].

In this review, we discuss methods to assist the differentiation of CD from UC. Furthermore, we provide an in-depth analysis of the available endoscopic techniques in diagnosing IBD. Lastly, we discuss the role of therapeutic endoscopy in the fibrostenotic phenotype of CD.

Clinical and pathological distinction between CD and UC

CD can involve any part of the GI tract from the oral cavity to the anal canal and perianal region. Studies have reported that approximately 28% of CD patients have isolated terminal ileitis, 50% have inflammation of the terminal ileum as well as the colon and 25% have isolated colonic disease [19, 20]. Furthermore, disease activity proximal to the ligament of Treitz occurs in up to 13% of patients with CD [21]. Macroscopic endoscopic features of CD include patchy disease activity, segmental colitis/enteritis, presence of strictures or fistulae and inflammation sparing the rectum. Stricturing of the ileocecal valve may lead to malnutrition and small-bowel bacterial overgrowth [22, 23]. Also, the presence of perianal fistula and anal skin tags is suggestive of CD. When chronic inflammation persists, a cobblestoning appearance may be evident on endoscopy [6]. Histologically, CD is characterized by transmural inflammation and granuloma formation. Architectural distortion and basal plasmacytosis may also be evident.

UC is characterized by consistent involvement of rectal mucosa. Approximately 32% of patients exclusively experience proctitis, 33% left-sided colitis and 35% pancolitis [24]. Historically, terminal ileitis was consistent with a diagnosis of CD. However, studies have demonstrated that UC patients may also experience a phenomenon termed 'backwash ileitis', occurring in up to 10% of patients [25]. Hence, extensive assessment of the ileum with biopsies is necessary to rule out CD ileitis. Backwash ileitis in UC is particularly common in patients with concurrent primary sclerosing cholangitis. Characteristic lesions consistent with a diagnosis of UC include inflammation involving mucosa, muscularis mucosae and superficial submucosa and erythema [26]. Chronic colonic mucosal hyperplasia due to repeated inflammation

ulceration and healing may develop into polyp formation, termed pseudopolyposis. Pseudopolyps of the colon are more frequent in UC than in CD [27].

Distinguishing between CD and UC is of importance in evaluating patients with clinical presentation suspicious for IBD due to differences in prognosis and therapeutic interventions. For example, restorative proctocolectomy with ileal pouch–anal anastomosis is the surgical treatment of choice for patients with medically refractory UC or UC-associated neoplasia and the procedure is contra-indicated if CD is suspected. The distinction between CD and UC can be difficult, as the extent of phenotypical presentation of each disease varies significantly. It is estimated that approximately 15% of patients with colitis may be classified as IBDU [6]. The diagnosis of IBDU may bear a worse prognosis than classic UC. The natural history of IBD, regardless of its subtypes, is characterized by persistent or periodic episodes of inflammation and ulceration resulting in scarring of intestinal tissue. In patients with CD, the disease process can evolve into stricture and fistula. Complications pursue and quality of life can be worsened over the course of the disease, resulting in a great financial burden on the patients as well as healthcare system [28].

Diagnosis of IBD and advancement in endoscopy

It is estimated that up to 15% of patients will have a change of diagnosis, initially classified as CD or UC, within the first year of diagnosis—a problem largely attributed to the overlap of endoscopic features between the two [29]. The very first diagnostic colonoscopy or index colonoscopy is most accurate for the assessment of disease extent and distribution. One of hallmarks for UC diagnosis is the presence of diffuse inflammation starting from the rectum, extending proximally. Crohn's colitis is often diagnosed based on segmental inflammation in the colon and/or rectal sparing on endoscopy and histology. However, segmental inflammation and rectal sparing can occur in patients with treated UC. Hence, an accurate endoscopic and histologic diagnosis of CD vs UC is required prior to drug therapy. Colonoscopy with mucosal biopsy is considered the gold standard for diagnosis [30–32].

Endoscopists have relied on tools such as ileocolonoscopy, flexible sigmoidoscopy and small-bowel follow-through (SBFT) to provide an accurate diagnosis for patients suspected of having IBD. Furthermore, mucosal histological analysis is critical in defining the severity of inflammation as well as distinguishing between transmural and superficial mucosal disease. Evidence suggests clinical symptoms of IBD do not correlate with the severity of endoscopic lesions, although the severity of mucosal lesions influences the natural history of the disease [33]. For example, it has been reported that colonoscopic finding such as deep ulceration involving greater than 10% of the mucosal surface in patients with CD is a significant risk factor for progression to colectomy [34, 35]. Often termed 'index ileocolonoscopy', the American Society for Gastrointestinal Endoscopy (ASGE) guidelines suggest that this procedure should be conducted before any therapeutic intervention with immunosuppressive agents, as it allows direct visualization of colonic and ileal mucosa [36, 37]. Furthermore, index ileocolonoscopy is essential in ruling out other disease processes that may present with similar symptomatology to IBD, such as infectious colitis and ileal tuberculosis [38, 39]. Of note, it is recommended that patients discontinue all non-steroidal anti-inflammatory drugs prior to ileocolonoscopy, as these can cause mucosal ulcerations similar to those described in IBD [40]. Data

on index ileocolonoscopy in differentiating between CD and UC have been consistent. In a prospective study of 357 patients with 606 colonoscopies, the procedure was able to accurately make the distinction in 89% of all cases [31]. Those patients with fulminant, severe colitis, for whom colonoscopies are contra-indicated, flexible sigmoidoscopy can be considered to establish a diagnosis of UC, with the obvious limitation of neglecting the terminal ileum and ruling out CD. Upper endoscopy is routinely not indicated unless symptoms of other diseases processes such as peptic ulcer disease are present. Despite the recommendation of ileocolonoscopy as the first-line endoscopic procedure in IBD, evidence has suggested that it may have low sensitivity in diagnosing mild or quiescent CD [41, 42]. Hence, endoscopic procedures such as VCE, CLE and Single Balloon enteroscopy (SBE) have emerged as effective and possibly more accurate techniques in diagnosing the different subtypes of IBD.

VCE was approved in 2001 and has gained popularity for evaluating small-bowel disease activity in CD patients [43]. VCE is able to detect deep ulcerations by transmitting images via an ingestible video camera [44, 45]. The advent of VCE has overcome the obstacle of isolated CD in the small bowel typically not seen by standard procedures such as ileocolonoscopy and SBFT [46]. Compared with the conventional endoscopic procedures, VCE has been shown to be either superior or non-inferior in visualizing the entire length of small-bowel mucosa [47–52]. One study that evaluated 80 patients with signs and/or symptoms of CD who underwent VCE, SBFT and ileocolonoscopy found that VCE was more effective than SBFT and equivalent to ileocolonoscopy in detecting small-bowel CD lesions ($p < 0.001$) [44]. In another study of 52 consecutive patients with suspected small-bowel CD, VCE had higher accuracy in detecting small-bowel lesions compared with magnetic resonance imaging (MRI) and double-contrast fluoroscopy (94% vs 78% vs 33%) [47]. Similarly, Hara et al. reported that VCE effectively diagnosed 71% ($n = 12$) of all CD patients compared with 65% ($n = 11$) with ileocolonoscopy [48]. However, Solem et al. compared VCE with computed tomography enterography (CTE), ileocolonoscopy and SBFT and reported that, although the sensitivity of VCE for detecting active small-bowel CD (83%) was similar to CTE (83%), ileocolonoscopy (74%) or SBFT (65%), the specificity of VCE (53%) was significantly lower than that of the other tests ($p < 0.05$) [49]. In contrast, more recent data from a prospective study including 21 CD patients reported that the specificity of VCE was equivalent to magnetic resonance enterography (MRE) and CTE (91% vs 86% vs 85%) [50]. Similarly, in the pediatric population, the sensitivity and specificity of VCE in diagnosing CD was 91% and 92%, respectively [52]. Finally, a meta-analysis performed by Dionisio and colleagues, including eight trials ($n = 236$) comparing VCE with ileocolonoscopy, four trials ($n = 119$) comparing VCE with CTE and four trials ($n = 123$) comparing VCE with MRE for diagnosis of small-bowel CD, concluded that VCE was superior to CTE, SBFT and ileocolonoscopy: VCE vs SBFT (52% vs 16%, $p < 0.0001$, 95% confidence interval [CI]: 16–48%); VCE vs CTE (68% vs 21%, $p < 0.00001$, 95% CI: 31–63%); and VCE vs ileocolonoscopy (47% vs 25%, $p = 0.009$, 95% CI: 5–39%) [53]. Interestingly, no benefit of VCE was established over MRE. Despite these promising results, ileocolonoscopy is still considered the first-line diagnostic test with VCE—an attractive alternative.

The role of VCE in diagnosing IBDU and assigning a specific diagnosis of CD vs UC has also been evaluated, although initial investigations have been inconclusive [54, 55]. It has been suggested that VCE should be considered in patients with UC especially after colectomy with atypical clinical features to rule out CD. The major limitations of VCE in IBD has been the concern

for retention in the small bowel due to stricturing CD, which is reported to be approximately 2.6%. Moreover, concern for delayed transit time and the ability of the capsule to reach the cecum has led to the introduction of real-time placement of the capsule in the duodenum by means of a snare under direct visualization with endoscopy to improve rates of complete small-bowel examination and diagnostic yield [56].

CLE is a recently developed technique that allows in-vivo differentiation of vascular architecture and changes in cellular pattern during endoscopy. Illumination of tissue with a laser beam results in reflection of fluorescence light, which is captured by the CLE. Fluorescent agents such as cresyl violet, acriflavine and intravenous fluorescein are used to provide images of lamina propria and intracellular spaces [57]. Two approved devices are available for CLE: an endomicroscope integrated into the distal tip of a colonoscope and a probe-based endomicroscope passed through the working channel. Preliminary data on the role of CLE in differentiating UC from CD concluded that CLE was as effective as conventional endoscopy in detecting mucosal changes consistent with UC [58]. One study including 73 UC patients reported that CLE was more accurate than colonoscopy in evaluating macroscopically normal-appearing mucosa ($p < 0.001$) [59]. Similarly, another study of 76 CD patients reported that CLE significantly improved the diagnosis of CD compared with standard colonoscopy [60]. To further assess the efficacy of CLE in differentiating UC and CD, Tontini et al. concluded that CLE accurately distinguished between disease-specific microscopic features such as crypt architectural abnormality, patchy inflammation and focal cryptitis [15]. Furthermore, since cell shedding and intrusion of intraluminal bacteria into the intestinal mucosa have been proposed as mechanisms for the pathogenesis of IBD, CLE was able to demonstrate significantly more intra-mucosal bacteria in patients with CD compared to controls [61]. Hence, CLE may play a future critical role in aiding in the diagnosis of IBD. The role of CLE in determining the actual subtype of IBDU has yet to be determined. Despite concerns for the complexity of this procedure and significant costs associated with training, CLE is an easy-to-learn diagnostic tool that can aid in the diagnosis of IBD [62].

SBE includes procedures such as single-balloon and double-balloon enteroscopy (DBE). Both techniques universally involve intubation of the small bowel for diagnostic and therapeutic interventions. Compared with VCE, the DBE allows targeted biopsies of diseased mucosa. Advantages of SBE include the ability to visualize the entirety of the small bowel including the terminal ileum, the ability for histological analysis and the ability for therapeutic interventions such as hemostasis and dilatation of strictures [63, 64]. In one study including 10 consecutive patients, DBE was able to diagnose CD in approximately 50% of patients suspected of having small-bowel disease, of which 80% of patients had proven disease by histopathology [65]. This result is consistent with previously reported diagnostic yield of DBE of up to 48% [66–68]. Reported complications of DBE include risk of perforation and bleeding, although they occur in only 1% of all DBE procedures [69]. In general, DBE is an invasive, costly procedure and, as such, is not recommended as first-line diagnostic modality in diagnosis of CD [70]. Future studies comparing DBE to VCE may be needed to determine the effectiveness of each procedure in diagnosing CD.

Advancements of endoscopy in the therapeutic intervention of IBD

The role of endoscopy has progressed beyond that of disease detection and complication surveillance. Endoscopy has been

utilized in CD to treat complications such as strictures and obstruction. Strictureing of intestinal tissue occurs mainly in CD at the terminal ileum, ileocecal valve or ileal anastomosis post-operatively and occurs in up to 33% of patients with CD after 10 years of diagnosis [71]. The pathophysiology resulting in strictures includes transmural inflammation that chronically results in mesenchymal cell proliferation and fibrosis [72, 73]. The severity of CD inflammation, duration of disease activity and ileal involvement are all risk factors in stricture formation [74]. Strictures that produce symptoms of obstruction usually require therapeutic intervention. Due to ineffective medical therapy, surgical resection of fibrotic strictures is often needed [75]. However, post-surgical stricture recurrence has been demonstrated in up to 34% of patients with CD [76]. Multiple resections put patients at risk of short-bowel syndrome, emphasizing the need for alternative treatments to surgical resections. Bowel sparing surgical techniques to avoid colonic resection such as stricturoplasties can be used. However, these procedures are also associated with significant stricture recurrence rates post-operatively [77].

Dilatation via through-the-scope (TTS) and DBE have emerged as potential therapeutic interventions for CD-associated strictures [78–90]. The minimally invasive nature of endoscopic balloon dilatation and the ability for symptom resolution make it an attractive replacement for surgical procedures in treating stricture complications. The first reported study of DBE and therapeutic dilatation of small intestinal CD strictures demonstrated an excellent success rate as well as the ability to characterize stricture anatomy by injecting contrast medium [78]. Thienpont et al. reported the immediate success of a first stricture dilatation to be 97%, with complication rates approaching 5% [79]. Singh et al. reported the first series of TTS balloon dilatations of 29 strictures on 17 patients and reported a technical success rate of 96.5%, with a stricture recurrence rate of only 10% [80]. Hirai et al. reported 25 patients who underwent endoscopic balloon dilatation with a success rate of 72% and surgery-free rate of 83% at 6 months post dilatation [81]. Another study by Gustavsson et al. reported a 52% stricture-free patient rate at 5 years after first endoscopic dilatation [82]. Despite promising and consistent results on endoscopic balloon dilatation, Hassan and colleagues concluded that we are unable to delineate the exact use of this procedure due to inconsistencies in each study, including varying balloon diameters, approaches and numbers of dilatations [91].

As stricture formation in the ileal pouch–anal anastomosis may be near 14%, there have been three studies on endoscopic dilatation of these complicating strictures [92–95]. Shen and colleagues performed endoscopic balloon dilatation on 19 patients with pouch strictures, with 100% success and no complications [92]. Similarly, in a large study of 150 patients with pouch strictures, 406 therapeutic endoscopies were performed, with a 0.46% perforation rate and 0.98% bleeding risk. The 5-year pouch retention rate was 97%, indicating a significant benefit of endoscopic treatment in retaining pouch function [93]. Wu et al. compared surgical stricturoplasty and endoscopic balloon dilatation in treating ileal pouch strictures and concluded that there was no significant difference between the two procedures in overall pouch survival [94].

Overall, a review of 23 publications on endoscopic dilatation of CD strictures reported an average success rate of up to 90% [96]. However, Ferlitsch et al. reported that recurrent symptoms after endoscopic dilatation of CD strictures resulted in a repeat of the dilatation in 62% of patients [86]. Therefore, to improve the accuracy of dilatation as well as reduce the requirements

for post-dilatation surgery at follow-up, factors that influenced the outcome of endoscopic balloon dilatation were determined. A length of stricture >5 cm and strictures of the terminal ileum were associated with poor response to endoscopic balloon dilatation. The effect of smoking on risk of surgery post dilatation has been inconclusive thus far. Interestingly, research has been conducted on azathioprine immunosuppressive therapy post dilatation, suggesting that this may prevent the recurrence of small intestinal strictures. Furthermore, intralesional steroid injection post endoscopic balloon dilatation has been extensively studied. Intra-lesional triamcinolone injections have not been effective at preventing rates of redilatation and surgery, although some studies suggest corticosteroid injection may be effective in reducing these complications [97, 98]. Complications of endoscopic balloon dilatation included bowel perforation, severe bleeding, abdominal pain and fever, occurring in up to 5.3% of all procedures. Perforation occurred in only 8 of approximately 1500 endoscopic balloon dilatations in one study. No mortality was reported from these complications. As such, dilatation through DBE offers as a promising first-line therapeutic intervention. Prospective, long-term clinical trials are needed to look at outcomes of patients who undergo DBE compared with surgery as a first-line intervention for strictureing CD.

In addition to endoscopic balloon dilatation, endoprosthetic management of strictures with self-expanding metal as well as biodegradable stents has been proposed [99, 100]. Although, individual case reports have demonstrated clinical success, larger studies have reported high rates of stent migration and limited clinical success. Attar and colleagues demonstrated six migrations out of 10 stent placements, as well as only one patient who remained symptom-free after 73 months [101]. As such, stent use is not routinely recommended for use with strictures in CD.

Other innovations in therapeutic endoscopy in IBD include the concept of direct application of medications to inflamed intestinal tissues. Initial studies investigating the delivery of micro-particles to inflamed tissue have offered promising results. Delivery of anti-inflammatory medications via micro-particles may increase the effectiveness of these medications and may enhance mucosal healing. However, currently, limited evidence exists for the role of intralesional biologics given the retrospective nature of most studies and small sample size [102, 103].

The role of endoscopic ultrasound (EUS) in patients with CD has recently been recognized, especially in patients with perianal disease [104–106]. In a prospective study including 25 patients, EUS was superior to computerized axial tomography scan in diagnosing fistulae (14 vs 4 correct diagnoses) and inflammatory infiltration of the lower pelvic muscles (11 vs 2 correct diagnoses) [104]. In another prospective study of 22 patients, the sensitivity of EUS and MRI as means for evaluating anorectal abscesses was 100% and 55%, respectively [105]. Furthermore, in another prospective study of 34 CD patients with suspected perianal fistula, the accuracy of three modalities was $\geq 85\%$: EUS 29 of 32 (91%, 95% CI: 75–98%), MRI 26 of 30 (87%, 95% CI: 69–96%) and EUA 29 of 32 (91%, 95% CI: 75–98%). Accuracy was 100% when any two tests were combined [106].

Another recent advancement in the field of IBD has been the introduction of chromoendoscopy for dysplasia surveillance [107]. It involves topical application of methylene blue or indigo carmine to colonic mucosa to provide contrast enhancement for the detection of subtle epithelial abnormalities. A recent meta-analysis of six studies involving 1277 patients reported the difference in yield of dysplasia between chromoendoscopy and white-light endoscopy to be 7% (95% CI: 3.2–11.3) on a per-

patient analysis with a number needed to treat of 14.3. The difference in the proportion of lesions detected by targeted biopsies was 44% (95% CI: 28.6–59.1) and flat lesions was 27% (95% CI: 11.2–41.9) in favour of chromoendoscopy [108].

Recently, the role of therapeutic endoscopy has also been explored in CD patients with abscess and fistula as either a bridge or alternative to surgery. The various approaches for fistula management include endoscopic fistulotomy or use of fibrin glue or plug. Similarly, for abscesses, endoscopy-guided pigtail stent placement may be a valid option. Furthermore, endoscopic clipping with as TTS clip and over-the-scope clip, suturing and covering of the fistula and anastomotic leak have also been studied. However, further studies with larger sample sizes are needed to establish their role in routine practice [109].

Summary and conclusions

Endoscopy has an important role in the diagnosis and treatment of IBD. Newer, non-invasive investigations can assist with the differentiation between CD and UC. Furthermore, the role of the therapeutic endoscopist in the domain of IBD has recently been recognized. Endoscopic balloon dilation or stenting of CD stricture to avoid recurrent surgery and short-bowel syndrome have become a common therapeutic practice in IBD. Additionally, recent recognition of the use of EUS in CD perianal fistulas and chromoendoscopy for dysplasia surveillance has broadened the horizon for these therapeutic techniques. In conclusion, therapeutic endoscopy has become an integral part of IBD and future research will further enhance its role in the early diagnosis, treatment of complications and early detection of neoplasia.

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