Advances in Endoscopy in Inflammatory Bowel Disease

Toshifumi Hibi
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Preface

Gastrointestinal endoscopy is indispensable for the treatment of gastrointestinal diseases. Its advances have been impressive; progress of diagnostic techniques and therapeutic procedures for neoplastic diseases in both the upper and lower gastrointestinal tracts has been especially remarkable. On the other hand, endoscopy has had a limited role in inflammatory diseases compared with neoplastic diseases, as it had been regarded solely as a tool for diagnosis. However, medical treatments and therapeutic strategies for patients with inflammatory bowel disease (IBD) such as ulcerative colitis and Crohn's disease have been revolutionized since the introduction of biologics including anti-TNF alpha antibodies. Many novel medical treatments have emerged targeted to control intestinal inflammation and correct abnormal immune response.

Endoscopy gradually has become more indispensable in the field of intestinal inflammation for the appropriate diagnosis and monitoring of the clinical course as medical treatments have become more complex and selection of the appropriate treatment is necessary. It has been my growing concern that there were only a few textbooks for endoscopy addressing this situation; however, now this new guide has been published as a useful textbook for inflammatory bowel disease clinicians. Fields of gastrointestinal endoscopy should be classified differently, into those for neoplasms and those for inflammation. A role of endoscopy for neoplastic diseases is to cover all the aspects from diagnosis to treatment, while less attention is paid to clinical symptoms, their course, or both. This book has been written by renowned specialists not only from Japan but also from other countries, and its main focus is on endoscopy for intestinal inflammation, especially for inflammatory bowel disease.

There are four main roles of endoscopy to treat patients with inflammatory intestinal diseases such as inflammatory bowel disease.

1. The first role of endoscopy is to serve as a diagnostic tool. Successful medical management of inflammatory bowel disease begins with an accurate diagnosis distinguishing it from other diseases by endoscopy in addition to obtaining a complete medical history and conducting thorough physical examinations and stool and blood tests.

2. The second role of endoscopy is to monitor the therapeutic response and clinical course. Making a judgment of whether to change, continue, or discontinue inflammatory bowel disease treatment by monitoring the disease state is crucial in treating inflammatory bowel disease. Moreover, endoscopy plays a vital role in accurately visualizing and assessing the disease state and helping in deciding the appropriate medical treatments for each patient. Recently, endoscopic mucosal healing is being emphasized as an objective factor that predicts favorable long-term prognosis.
3. Moreover, endoscopy is necessary for the appropriate surveillance of colitis-associated cancer.
4. Finally, endoscopic interventions play important roles in endoscopic dilation technique for strictures and hemostasis for bleeding, similar to endoscopy for neoplastic diseases.

This book focuses on the four roles of endoscopy for inflammation, and it contains abundant endoscopic pictures by some of the world's top specialists, particularly in Asia. I hope the book will be useful in daily clinical practice for treating patients with inflammatory intestinal diseases.

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Part I
The Role of Endoscopy in IBD

Chapter 1
The Role of Endoscopy in Inflammatory Bowel Disease

Haruhiko Ogata

Abstract Endoscopic assessment of mucosal lesions has emerged as an important concept of disease activity in inflammatory bowel disease (IBD), and recently mucosal healing has generally been regarded as a therapeutic goal not only in ulcerative colitis (UC) but also in Crohn's disease (CD). Several pieces of evidence have now accumulated to show that mucosal healing determined by endoscopy can alter the course of IBD, as it is associated with sustained clinical remission, and reduced rates of hospitalization and surgical resection. Generally, clinical activity indices established in IBD are mainly determined based on subjective/objective signs and the results of laboratory tests. However, those indices sometimes lead to discrepancy compared with endoscopic indices. Although endoscopy has been rarely investigated as a predictor of the clinical course of IBD, there is now growing evidence that morphological examination, including endoscopy, may help to identify among IBD patients those who should be treated with more intensive treatments. Furthermore, as demonstrated in a recent study assessing early intervention with combination of biologics and immunomodulators, endoscopy may help to select patients who will obtain the best results with early intervention. This chapter summarizes the role of endoscopy in IBD by introducing several modalities such as colonoscopy, balloon-assisted enteroscopy, and video capsule endoscopy, as well as CT colonography and MR enterography.

Keywords Inflammatory bowel disease • Ulcerative colitis • Crohn's disease, endoscopy • Mucosal healing • Activity indices • Medical therapy • Surgery

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1.1 Introduction

The management of ulcerative colitis (UC) and Crohn's disease (CD), the two major forms of inflammatory bowel diseases (IBD), has dramatically changed over the last decade. Progress has been supported by the increasing evidence from therapeutic strategies, the introduction of biologics providing more alternative options in patients with severe diseases, and new concepts as to how and when treatments should be used [1, 2]. Immunomodulators and biologics are classically used following a step-up approach in patients with refractory disease, who are unresponsive to conventional therapies or are steroid-dependent. Beyond their high efficacy in induction and maintenance of remission, it has been demonstrated that anti-tumor necrosis factor (TNF) therapies can close fistulae and heal mucosal lesions, and reduce rates of hospitalization and surgery [3]. Several recent studies suggest that early intervention with combination therapy may modify the long-term course of CD [4–6]. Meanwhile studies performed with regard to prediction of the disease activity have mainly focused on clinical and biological parameters, and endoscopy has been rarely investigated as a predictor of the clinical course of IBD. However, there is now growing evidence that morphological examination, including endoscopy, may help to identify among IBD patients those who should be treated with more intensive treatments. Furthermore, as demonstrated in a recent study assessing early intervention with combination of infliximab and azathioprine in CD, endoscopy may help to select patients who will obtain the best results with early intervention [4].

Endoscopic assessment of mucosal healing is usually assessed by colonoscopy in patients with UC. In fact, there are several indices proposed to measure endoscopic severity in UC (see Chap. 16); however, they have not been fully validated, and are subject to inter-observer variation. Recently, the development of a validated ulcerative colitis index of severity (UCEIS) has been established, and the American Gastroenterological Association is going to provide a forum for discussing the possibility of design and interpretation of future clinical trials in UC using UCEIS (see also Chap. 16). Meanwhile, the assessment of mucosal healing of CD has been performed by ileocolonoscopy, and recently balloon-assisted small-bowel enteroscopy and video-capsule endoscopy have also contributed to the evaluation of disease activity of small-bowel CD (see Chap. 17). Furthermore, CT-guided colonoscopy (virtual colonoscopy) and MR enterocolonoscopy also have contributed to diagnosis, monitoring, and therapy against IBD. In this chapter, the overview of important aspects of bowel involvement in IBD is discussed.

1.2 Feasibility of Endoscopy in Active UC

Carbonnel et al. [2] demonstrated that total colonoscopy is feasible in 86% of cases of severe UC (73/85). In this study, endoscopy accurately identified severe endoscopic lesions (extensive deep ulcerations). Eighty-five consecutive patients with

attacks of UC were reviewed. Extensive deep colonic ulcerations were diagnosed in 46 of them. No complication related to colonoscopy occurred except for one colonic dilatation. Forty-three of the 46 patients with severe endoscopic colitis underwent surgery. Extensive ulcerations reaching at least the circular muscle layer were found on pathological examination, and were confirmed in 42/43 of cases [7]. Because of potential risks of complications, some rules have to be applied when performing colonoscopy in patients presenting severe attacks of UC, including pre-radiological examination to exclude megacolon and minimal insufflations; and when severe lesions are detected, the examination can be stopped as further examination has no additional prognostic value.

1.3 Mucosal Healing Evaluated by Endoscopy Contributes to a Better Outcome in UC

To date, there is no consensus on the definition of mucosal healing in UC [1]. The International Organization of IBD proposed the following definition: absence of friability, blood, erosions, and ulcers in all visualized segments of the gut mucosa. According to this definition, disappearance of the normal vascular pattern is compatible with mucosal healing [1, 3]. It has been shown that mucosal healing can be obtained with 5-aminosalicylates (5-ASA), steroids, azathioprine or methotrexate, and infliximab. Mucosal healing has been assessed in recent trials with different formulations of 5-ASA. In the ASCEND studies, evaluating different dosages of a delayed-released oral mesalazine in patients with mild or moderate UC, complete remission (including endoscopic remission) ranged between 18% and 25% at week 6 [4, 10]. Truelove et al. [5] demonstrated in 1954 that mucosal healing can be obtained with a high-dose of oral steroids in 30% of patients at week 6, compared with 10% in patients who received placebo ($P = 0.02$). In a recent review, it was considered that corticosteroids induce mucosal healing in 12–41% of patients with UC, depending on the method of administration and the medication [1]. Some data suggest that mucosal healing may also be obtained with azathioprine or methotrexate [6, 13]. Anti-TNF agents probably induce mucosal healing more rapidly. In ACT 1 and ACT 2, patients with refractory moderate-to-severe UC received placebo or infliximab intravenously [14]. Induction therapy with infliximab resulted in mucosal healing at week 8 in 61% of patients (148/242) compared with 32% (79/244) in the placebo groups ($P < 0.001$) [14]. At week 54 (ACT 1), scheduled maintenance therapy with infliximab resulted in mucosal healing in 45.5% (55/121) of patients compared with 18.2% (22/121) in the placebo group ($P < 0.001$). Data from several studies suggest that mucosal healing may be associated with a better outcome in UC, more specifically a decreased risk of relapse. Reduced relapse rates have been demonstrated in UC patients who achieved mucosal healing with steroids. In a study published in 1966, Wright et al. [7] found that 40% of patients who achieved mucosal healing with oral and rectal steroids did not relapse during 1 year of follow-up, as compared to 18% of those who still had lesions. In the ACT1 and ACT2 studies

on infliximab maintenance in patients with moderately to severely active UC, 48.3% of the patients who achieved mucosal healing at week 8 were in remission at week 30, as compared to only 9.5% of those who did not achieve mucosal healing [13]. Mucosal healing may also be associated with reduced risk of surgery in UC. In the IBSEN population-based study, UC patients who achieved mucosal healing at 1 year (whatever the treatment) had a decreased risk of colectomy at 5 years (2% vs 7%, $P = 0.02$) [16]. A study performed in the Leuven cohort of UC patients treated with infliximab showed that colectomy was more frequent in patients who did not achieve mucosal healing at week 4 or 10 (Mayo endoscopic subscore greater than 1) [17]. In ACT1 and ACT2, it was shown that patients treated with infliximab were less likely to undergo colectomy through 54 weeks than those receiving placebo [18]. However, data on the relationship between mucosal healing and risk of colectomy are not available in these studies. Finally, there is a clear relationship between the grade and chronicity of inflammation in the colon and the risk of colorectal cancer. Better control of inflammation, as demonstrated with mucosal healing, may be associated with decreased risk of colorectal cancer.

1.4 Endoscopic Severity of UC Contributes to an Increased Risk of Colectomy

Among patients hospitalized for a severe attack of UC, the presence of extensive and deep ulcerations at colonoscopy is associated with an increased risk of colectomy on that admission [7]. In their study performed in the prebiologic era, Carbonnel et al. [2] showed that colectomy was performed in 43 of the 46 patients who presented severe endoscopic lesions (93%), as compared to 10/39 (26%) of those without such lesions (OR 41). In another study performed in severe UC patients, severe endoscopic lesions at colonoscopy were significantly more frequent in non-responders to medical treatment (91%) compared with responders (34%) (OR >20) [19]. The colonoscopies performed during severe attacks of UC also have an impact on the long-term outcome, with an increased rate of surgery in the long term in patients who exhibit extensive and deep ulcerations at index colonoscopy [20]. Namely, although intravenous cyclosporine treatment could exert high initial efficacy for severe attacks of UC, 50% of patients who had relapse required a colectomy. Specifically, mucosal healing evaluated by a novel endoscopic activity index [8] at day 14 after cyclosporine injection was associated with the 1-year colectomy rate [21].

1.5 Severe Mucosal Lesions of Colonic CD Evaluated by Endoscopy

Severity of colonic lesions in CD relies on the extent in depth and in surface of the mucosal damage. A previous interobserver variation study targeted on evaluation of ileocolonoscopic lesions in CD [9] has shown that deep ulcerations and estimation of

ulcerated surface were among the most reproducible endoscopic items. Such lesions were also selected by multivariate analysis for the construction of the CDEIS [22]. Nahon et al. [10] demonstrated that colonoscopy accurately predicts the anatomical severity of colonic CD attacks. In this retrospective study of 78 patients operated for colonic CD resistant to medical treatment, criteria of severity in colectomy specimens were defined as either deep ulcerations eroding the muscle layer, or mucosal detachments, or ulcerations limited to the submucosa but extending to more than one third of one defined colonic segment (right, transverse, left colon). Three endoscopic criteria of severity were defined: (a) deep ulcerations eroding the muscle layer, (b) deep ulcerations not eroding the muscle layer but involving more than one third of the mucosal area, and (c) mucosal detachment at the edge of ulcerations. Evaluation of endoscopic severity correlated well with findings on colectomy specimens. At least one of these criteria was found in 95% of patients with severe anatomic lesions on colectomy specimens. The extent of ulcerations at colonoscopy was correlated to the results of colectomy specimen examination ($P < 0.001$). This study further demonstrates that colonoscopy can accurately assess anatomical severity of colonic CD.

Endoscopic severity may have an impact on the long-term course of the disease. Allez et al. [11] showed in a retrospective study that patients with CD exhibiting deep and extensive ulcerations at colonoscopy have a more aggressive clinical course with an increased rate of penetrating complications and surgery. Among the 102 patients included, 53 had severe endoscopic lesions at index colonoscopy, defined as extensive and deep ulcerations covering more than 10% of the mucosal area of at least one segment of the colon. During the follow-up (median 52 months), 37 patients underwent colonic resection. Furthermore, patients with severe endoscopic lesions needed significantly more colonic resections than patients without severe lesions [23]. These data suggest that a subset of CD patients have a more aggressive disease, characterized by severe endoscopic lesions in the ileocolon during symptomatic phases, and a higher risk of surgery [23].

1.6 Mucosal Healing Evaluated by Endoscopy after Medical Treatment against CD

Therapeutic effect in clinical trials against CD is usually assessed by improvement defined by a decrease of the CDAI. Assessment of endoscopic improvement was not usually performed until recently in clinical trials assessing the efficacy of drugs in CD. The main reason for this was that steroid-induced clinical remission is not associated with mucosal healing in two-thirds of CD patients. However, there is growing evidence that mucosal healing during therapy is a sign of a good efficacy of a drug [1, 24]. Data from the IBSEN cohort strongly suggests that mucosal healing predicts a generally favorable outcome of disease based on all types of treatment strategies, and is related to treatment efficacy, reduced frequency of surgery and hospitalizations [16]. Moreover, it is now clearly demonstrated that mucosal healing can be achieved with azathioprine and anti- TNF [25–29]. Rates of mucosal healing under azathioprine vary among studies, probably due to differences in the timing of

endoscopy and the population analyzed. In a randomized controlled trial performed in steroid-dependent CD patients, Mantzaris et al. [12] have recently shown that azathioprine was superior to budesonide in inducing mucosal healing at 1 year; complete or near complete healing was achieved in 83% of azathioprine-treated patients compared with only 24% of budesonide-treated patients ($P < 0.0001$). In a GETAID study, long-lasting remission (≥42 months) maintained with azathioprine was associated with a complete mucosal healing (CDEIS = 0) in only 36% of CD patients [30]. In the SONIC study, which concerned CD patients naïve to immunomodulators and biologics, only 15.6% of patients treated with azathioprine achieved mucosal healing at week 26 [4]. In the endoscopic substudy of the ACCENT I study, patients treated with scheduled maintenance therapy with infliximab had superior rates of mucosal healing, and those who maintained complete mucosal healing over 1 year had a lower rate of hospitalizations and surgeries [13, 31]. A study of mucosal healing in a cohort of CD patients under long-term treatment with infliximab was recently reported [32]. In this study from the Leuven group, 214 patients had a colonoscopy before and a second one within months after starting infliximab. Mucosal healing was observed in 68% of the 183 initial responders. Mucosal healing was associated with a significantly lower need for major abdominal surgery during long-term follow-up (14.1% major surgeries in patients with mucosal healing vs 38.4% in patients without mucosal healing, $P < 0.0001$). Several studies suggest that immunomodulators and anti-TNF therapy may be more effective when given early in the course of the disease. Recently there are two studies of "top-down" therapy performed in CD patients naïve to immunomodulators and biologics, which refers to early introduction of immunosuppressive or biologic therapies. In the SONIC study, infliximab therapy was superior to azathioprine in inducing mucosal healing at week 26 (30.1% vs 15.6%), but inferior to infliximab plus azathioprine combination therapy [4]. D'Haens et al. [14] compared a top-down strategy to a more classical step-up strategy. Top-down strategy, which consisted of early induction with infliximab and maintenance with azathioprine, resulted in mucosal healing in 19/26 of patients (73%) at week 104. In the other arm (step-up strategy), mucosal healing was significantly less frequent (7/23 patients, 30%). Additionally, when mucosal healing was achieved at 2 years (SES-CD score at 0), 70% of the patients (17/24) were in stable clinical remission during the following 2 years as compared to only six of the 22 (27%) who had mucosal lesions (SES-CD score above 0) [6]. Fifteen of the 17 patients with mucosal healing at year 2 maintained in remission without further infliximab infusions during the following 2 years. Furthermore, mucosal healing obtained with immunomodulators or anti-TNF agents was also associated with a decreased risk of surgery in the long term. Altogether, these data would suggest checking endoscopic response in patients treated with immunosuppressants or anti-TNF. In a placebo-controlled study by GETAID, presence of ulcerations at ileocolonoscopy before withdrawal of azathioprine was not predictive of the risk of relapse [30]. A recent study from GETAID assessed the risk of relapse after infliximab discontinuation in patients in remission on combined maintenance therapy, who continued the immunosuppressant (azathioprine or methotrexate). Mucosal healing was among the factors strongly associated with a decreased risk of relapse [33].

1.7 Endoscopic Assessment Contributes in Predicting Relapses of CD after Surgery

It is generally accepted that CD patients who have ileal resection and ileocolonic anastomosis are exposed to a high risk of postoperative recurrence [34]. Rutgeerts et al. [15] demonstrated that ileocolonoscopy performed within 1 year of surgery may predict the risk of clinical recurrence. Eighty-nine patients treated by ileal resection for CD were included in this prospective cohort follow-up to study the natural course of early postoperative lesions. Within 1 year of surgery, ileocolonoscopy detected recurrent lesions in the neo-terminal ileum in 73% of the patients, although only 20% had a clinical relapse. The rate of clinical relapse was 34% at 3 years. A score was devised to assess the severity of recurrent endoscopic lesions. The course of the disease was best predicted by the severity of the early postoperative lesions, as observed at ileocolonoscopy, on the anastomosis and/or on the neoterminal ileum. Indeed, patients with less severe endoscopic lesions according to Rutgeerts' score (less than five aphtoid ulcers at anastomosis site), have a lower risk of clinical recurrence risk at 9% compared with 100% risk at 4 years for patients with more severe endoscopic recurrence (Rutgeerts' score i2 or greater). This score is widely used in clinical practice, and ECCO guidelines state that ileocolonoscopy should be the gold standard for the diagnosis of postoperative recurrence by defining the presence and severity of morphologic recurrence and predicting the clinical course. Ileocolonoscopy is recommended within the first year after surgery where decisions of postoperative treatment may be affected [35]. Furthermore, recently Regueiro et al. [16] showed that administration of infliximab soon after intestinal resection was effective at preventing endoscopic recurrence of CD. They randomly assigned 24 CD patients who had undergone ileocolonic resection to receive intravenous infliximab, administered within 4 weeks of surgery and continued for 1 year, or placebo. The rate of endoscopic recurrence at 1 year was significantly lower in the infliximab group (one of 11 patients; 9.1%) compared with the placebo group (11 of 13 patients; 84.6%) ($P = 0.0006$).

1.8 Conclusion

In patients with active IBD, endoscopy may help to select patients who should receive early and active therapies. One reason is that severe endoscopic lesions may predict a poor outcome with increased risk of colectomy and complications. Next, patients with no lesions gain no benefit in receiving active treatments with potential risks. In treated IBD patients, mucosal healing is associated with a better outcome, with decreased risks of relapse and major surgery. Assessment of mucosal healing may help to characterize the response to treatments and in decisions of optimal strategies. Finally, endoscopy, which allows a direct assessment of severity and extent of mucosal lesions, may thus help in the management of IBD.

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