



Magnifying chromoscopy, a novel and useful technique for colonoscopy in ulcerative colitis

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Abstract

Ulcerative colitis (UC) is a chronic inflammatory bowel disorder characterized by exacerbations and remissions. The degree of inflammation as assessed by conventional colonoscopy is a reliable parameter of disease activity. However, even when conventional colonoscopy suggests remission and normal mucosal findings, microscopic abnormalities may persist, and relapse may occur later. Patients with long-standing, extensive ulcerative colitis have an increased risk of developing colorectal cancer. Ulcerative colitis-associated colorectal cancer is characterized by an early age at onset, poorly differentiated tumor cells, mucinous carcinoma, and multiple lesions. Early detection of dysplasia and colitic cancer is thus a prerequisite for survival. A relatively new method, magnifying chromoscopy, is thought to be useful for the early detection and diagnosis of dysplasia and colitic cancer, as well as the prediction of relapse.

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INTRODUCTION

The degree of inflammation in ulcerative colitis (UC)

as assessed by conventional colonoscopy is a reliable parameter of disease activity. Even when conventional colonoscopy suggests remission and normal mucosal findings, however, microscopic abnormalities may persist^[1,2], and relapse may occur later^[3]. UC is a chronic disease with an unknown cause characterized by diffuse mucosal inflammation of the colorectum and a course of exacerbations and remissions^[4-8]. The purpose of treatment in patients with UC is thus the achievement of remission and maintenance of quiescence. An important factor in choosing treatment methods is the evaluation of disease activity; this is commonly done using clinical criteria based on symptoms^[9] owing to its convenience and noninvasiveness. When clinical criteria are used alone, however, 40% of patients in whom remission is achieved relapse within 1 year^[10,11]. This finding indicates the need for colonoscopic and histopathologic assessment also, notwithstanding their disadvantages, including inconvenience, invasiveness and prolongation of the colonoscopic examination.

Patients with long-standing UC are known to have an increased risk for the development of colorectal cancer. Although some investigators recommend prophylactic total proctocolectomy for these high-risk patients, surveillance colonoscopy to detect UC-associated colorectal cancer is generally performed instead. Although UC-associated dysplasia is considered a useful marker of colorectal cancer at surveillance colonoscopy, recognition of dysplasia, particularly flat dysplasia, is hampered by the inflammation-induced granular changes which arise in background mucosa. It is therefore generally recommended that biopsy specimens be taken every 10 cm along the whole colorectum^[12]. Even with this coverage, however, a set of 10 biopsy specimens has been theoretically calculated to represent only 0.05% of the total surface area of the whole colorectum^[13].

Of interest, recent reports have indicated that careful mucosal examination aided by chromoendoscopy and magnifying endoscopy, and target biopsies of suspicious lesions might provide more effective surveillance than the taking of multiple non-targeted biopsies^[14-16].

EVALUATION OF ULCERATIVE COLITIS

Histopathologic assessment of UC

Severity in ulcerative colitis is generally assessed using symptoms, laboratory data^[17], colonoscopic findings^[2,18-25] and the histologic degree of inflammation in the biopsy specimens^[3,26-29]. Of these, histopathologic assessment

is considered the standard for evaluation of disease activity^[30]. Observation under conventional colonoscopy is regarded as useful for the evaluation of disease activity, since it offers direct observation of mucosal changes, but it remains controversial whether colonoscopic grade correlates with histopathologic findings. Notably, the degree of histologic inflammation within biopsy specimens does not necessarily correlate with endoscopic abnormalities^[1,2,18,25,31].

Are magnifying chromoscopic findings useful for the evaluation of UC?

Matsumoto *et al*^[14] reported the usefulness of magnifying chromoscopy in the assessment of severity. Magnifying colonoscopy was performed in 41 patients with ulcerative colitis, with findings in the rectum graded according to network pattern (NWP) and cryptal opening (CO). The clinical, endoscopic and histologic grades of activity did not differ between groups categorized by the presence or absence of each finding. However, when the two features were coupled, patients with both visible NWP and CO had a lower clinical activity index and lower grade of histologic inflammation than those in whom neither finding was seen. Further, the presence of breaches in surface epithelium may be an additional factor in future relapse^[3], and an altered pattern as defined by magnified colonoscopic views may be predictive of course^[14].

Fujiya *et al*^[15] proposed a classification system for magnifying colonoscopic findings in patients with UC which has proved useful for the evaluation of disease activity and prediction of periods of remission. This classification references regularly arranged crypt openings, a villous-like appearance, minute defects of epithelium (MDE), small yellowish spots (SYS), and a coral reef-like appearance. Colonoscopic findings under this classification were compared with histopathologic findings in 61 patients and the usefulness of the classification for predicting relapse was prospectively analyzed in 18. Under conventional colonoscopic examination, all areas evaluated as Matts' grade 1 had a corresponding histopathologic grade of 1. In contrast, most areas assessed as Matts' grade 3 or 4 were diagnosed as histopathologic grade 3 or higher. In contrast, Matts grade 2 mucosa had histopathologic findings that varied from quiescent to active disease. These results suggest that while normal and diseased mucosa are easily recognized by conventional colonoscopy, assessment of the minute mucosal changes that reflect smoldering histopathologic inflammation is much less successful^[1,2,18]. Under magnifying colonoscopic examination, in contrast, 37 (82.2%) of the 45 areas in which regularly arranged crypt openings or a villous-like appearance was detected had a corresponding histopathologic grade of 1, while all areas with MDE, SYS, or the coral reef-like appearance had a corresponding histopathologic grade of 2 or higher. In particular, the correlation between histopathologic grade and magnifying colonoscopic findings ($r^2 = 0.807$) was better than that for histopathologic grade versus conventional colonoscopy ($r^2 = 0.665$). This study found that patients in whom MDE was observed during clinical remission frequently experienced relapse within short periods (6 mo) compared with those without this finding,

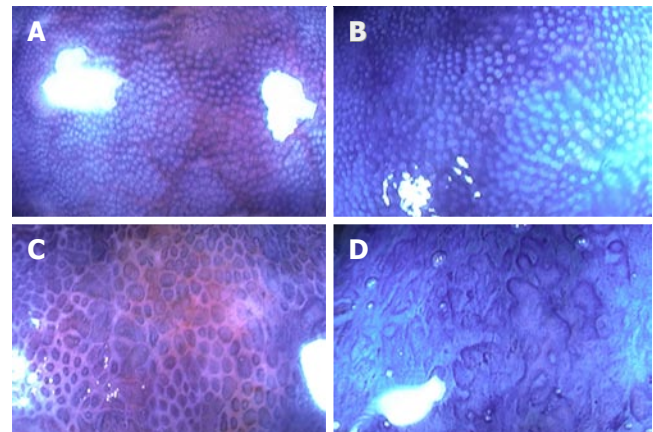


Figure 1 Grading of pit structures in the colorectal mucosa of patients with inactive UC. MCS grade 1: Pits are small, round, and regularly arranged (A). MCS grade 2: Pits are rather large, oval, and somewhat irregular in arrangement (B). MCS grade 3: Pits are of various shapes and sizes, and irregularly arranged (C). MCS grade 4: Dispersed pits vary in morphology and are associated with the presence of small erosions (D).

and that 50% of patients who underwent clinical remission still had active inflamed mucosa with MDE^[15]. This latter finding correlates with a previous finding that 30% to 60% of patients in remission as determined by clinical symptoms were still in the active stage of ulcerative colitis based on histopathologic findings^[18,31].

Magnifying chromoscopic findings and prediction of relapse

Nishio *et al*^[16] reported that magnifying-colonoscopy (MCS) grade was associated with the degree of histological inflammation and mucosal IL-8 activity in quiescent patients with ulcerative colitis, and might predict the probability of subsequent disease relapse in patients with ulcerative colitis in remission. Magnifying colonoscopy was performed in 113 patients in remission, and the relationship between pit patterns, IL-8 activity, and histological disease activity was evaluated. Pit patterns in the rectal mucosa were classified into four MCS grades on the basis of size, shape, and arrangement (Figure 1). The patients were then followed until relapse or for a maximum of 12 mo. Results showed a positive correlation between MCS grade, histological grade, and mucosal IL-8 activity. Multivariate proportional hazard model analysis showed that MCS grade was a significant predictor of relapse. Moreover, the Kaplan-Meier estimate of relapse during 12 mo follow-up was found to increase with increasing MCS grade, with percentages of 0% for grade 1, 21% for grade 2, 43% for grade 3, and 60% for grade 4. Although MCS grade positively correlated with histological grade and mucosal IL-8 activity, these latter parameters were less accurate predictors of relapse. One reason may be that they are assessed in biopsy specimens derived from a specific and limited area of colorectal mucosa, whereas magnifying colonoscopy allows the observation of a more extended and representative area, and accordingly greater accuracy by MCS grading^[16]. These findings demonstrate the usefulness of MCS in the evaluation of disease activity and in predicting relapse in patients with ulcerative colitis.

UC-ASSOCIATED COLORECTAL CANCER AND DYSPLASIA

Colorectal cancer was first recognized as a complication of UC by Crohn and Rosenberg in 1925^[32]. UC-associated colorectal cancer differs from sporadic colorectal cancer in a number of ways: it is more common in younger patients^[33]; more frequently located in the proximal colon^[33]; difficult to detect by barium enema or even by colonoscopy due to its widespread nature^[34]; has mucinous and signet-ring histopathological features in approximately half of cases^[35]; and is genetically different from the adenoma-carcinoma sequence, with a dysplasia-carcinoma sequence now postulated^[36]. Many reports have demonstrated that dysplasia is a useful marker of UC-associated colorectal cancer. The object of surveillance colonoscopy is the detection of dysplasia, particularly a dysplasia-associated lesion or mass (DALM)^[37,38]. A classification for UC-associated dysplasia established by the IBD study group in 1983 categorized high-grade dysplasia (HGD), low-grade dysplasia (LGD), indefinite dysplasia (IND) and negative^[39]. IND is further classified into three categories: probably negative, unknown and probably positive.

Risk factors for UC-associated colorectal cancer

The risk of colorectal cancer is increased in patients with UC, particularly patients who have more extensive colorectal inflammation^[31,40], and those with a longer duration of colitis^[41-43] have the greater risk. Some reported that patients with an onset of colitis early in life are thought to have a greater risk than older-onset patients^[31,42,44]. Further, a recent study by Rutter *et al.*^[45] has shown that the severity of colonic inflammation is also highly significant in terms of neoplasia risk.

Purpose of surveillance colonoscopy for high-risk patients with UC

The purpose of surveillance colonoscopic examinations for patients with UC is the detection of colorectal cancers as early as possible, and prevention of cancer-associated death. One study found that patients with UC-associated colorectal cancer of Dukes' A and B showed good survival, whereas those of Dukes' C showed an extremely poor prognosis^[46].

When and how frequently should surveillance colonoscopy be performed?

UC-associated colorectal cancer is rarely encountered when disease duration is less than 8-10 years, but risk rises thereafter at approximately 0.5% to 1.0% per year^[47]. Most cancers arise in pancolitis, and it is generally agreed that there is little or no increase in risk associated with proctitis and an intermediate risk with left-sided colitis^[31,42]. A Swedish group performed a population-based study composed of 3117 patients with ulcerative colitis and concluded that those with total colitis have a far higher risk for the development of colorectal cancer than those with left-sided colitis^[31]. In contrast, other reports state that patients with left-sided colitis share the same risk as those with total colitis^[48,49] and that disease progression

should be taken into consideration^[50,51]. Guidelines from the World Health Organization (WHO)^[12] and American Gastroenterological Association^[52] recommend that patients with pancolitis undergo surveillance colonoscopy at 8 years after onset and those with left-sided colitis at 12-15 years. The recommended interval of surveillance colonoscopy varies by report or guideline as either annual or biannual. Annual colonoscopy will double the cost but may increase sensitivity as compared to biannual colonoscopy. Moreover, an additional consideration is that UC-associated colorectal cancer may advance faster than sporadic colorectal cancer. The answer to this question awaits a cost-benefit analysis^[53].

What is effective surveillance colonoscopy?

Following initial evidence that dysplasia, a precursor of cancer, may arise in flat mucosa, and presents as a widespread "field effect" distant to cancer sites in 96%-100% of cases^[54,55], surveillance protocols recommend the detection of dysplasia by multiple non-targeted random biopsies throughout the colon. The American Society for Gastrointestinal Endoscopy Guidelines advise taking two to four non-targeted biopsies for every 10 cm of colon and rectum^[56]. It is still believed that dysplasia is invisible at endoscopy^[57], but some reports state that magnifying chromoscopic examination is useful for detecting that occurring in ulcerative colitis^[58-60]. Kiesslich *et al.*^[61] reported that methylene blue-aided chromoendoscopy in UC surveillance was about three times more useful than conventional colonoscopy for detecting dysplasia, while Rutter *et al.*^[58] reported the usefulness of pancolonial indigo carmine dye spraying. The latter investigators compared biopsies of visible abnormalities and non-targeted biopsies taken every 10 cm during a first conventional colonoscopic examination with biopsies of any additional visible abnormalities during a second chromoscopic examination^[58]. No dysplasia was detected in 2904 non-targeted biopsies. In comparison, targeted biopsy protocol with pancolonial chromoendoscopy required fewer biopsies (157) yet detected nine dysplastic lesions, seven of which were only visible after indigo carmine application. There was a strong statistical trend towards increased dysplasia detection following dye spraying. Careful mucosal examination aided by pancolonial chromoendoscopy and targeted biopsy of suspicious lesions may therefore represent a more effective surveillance methodology than the taking of multiple non-targeted biopsies^[58]. Further, Hurlstone *et al.*^[60] observed intraepithelial neoplasia (IN) in flat mucosal change in 37 lesions, of which 31 (84%) were detected using High-Magnification-Chromoscopic-colonoscopy (HMCC), and HMCC significantly increased diagnostic yield for IN compared to conventional colonoscopy ($P < 0.01$).

MCS and pit pattern diagnosis have been widely used in Japan for non-colitic dysplasia lesions. This method is useful in differentiating invasive carcinoma (Type III_s, V pit pattern), adenoma (Type III_L, IV pit pattern), and hyperplastic polyp (Type II pit pattern)^[62]. Hata *et al.* examined surgical specimens of UC-associated colorectal cancer by stereomicroscopy, and compared the pit pattern with histopathology. In their study, Type III_L, IV and V pit

patterns corresponded well to dysplastic lesions, while the type I pit pattern corresponded to nondysplastic lesions^[59]. Hurlstone *et al*^[60] also emphasized high correspondence between pit pattern using HMCC and histopathology in ulcerative colitis. However, UC-associated colorectal cancer arises in the particular environment of ulcerative colitis, and slight deviations in pit pattern of the mucosa may be difficult to distinguish from epithelial regeneration. Further, UC may also be associated with complex pit patterns of the mucosa that cannot be classified according to the criteria of Kudo^[63]. These problems seriously hamper the application of pit pattern diagnosis to UC-associated colorectal cancer surveillance.

On the other hand, some investigators doubt the effectiveness of surveillance colonoscopy in terms of early detection, survival and cost^[64,65]. Axon *et al*^[66] reviewed 12 studies of colonoscopic cancer surveillance and criticized its effectiveness. In their review, 92 of 1916 patients were found to have cancer and only 52 (57%) were in Dukes' A or B. Patients with UC-associated colorectal cancer of Dukes' A or B showed a good survival rate, while those of Dukes' C had an extremely poor prognosis^[46]. Further, 476 colonoscopies were needed to detect one UC-associated colorectal cancer. The cost-effectiveness of surveillance colonoscopy remains questionable^[65-67]. Careful mucosal examination aided by chromoscopy and MCS may be more effective than that by conventional colonoscopy. Although its effectiveness has not been established in terms of cost and survival, surveillance colonoscopy should be performed for patients with long-standing ulcerative colitis until novel methods are established.

Management of dysplasia

While high grade dysplasia is an absolute indication for total proctocolectomy, management of low grade dysplasia is controversial. Some authors believe that LGD is a useful marker in the detection of UC-associated colorectal cancer. Nugent *et al*^[48] reported that 4 of 10 patients with LGD were found to have cancer, and another 2 had HGD in colectomy specimens. Woolrich *et al*^[68] reported that 18% of patients with LGD later developed invasive cancer, and recommended careful follow-up of these patients. Bernstein reported that 29% of LGD patients showed progression at some time to HGD, DALM, or cancer. Further, he reported that patients with LGD had a 19% probability of having cancer at immediate colectomy, and asserted that the finding of definite dysplasia of any grade was an indication for colectomy^[64]. Moreover, the St Mark's Hospital surveillance study indicated the 5-year predictive value of LGD for either HGD or cancer was 54% and recommended that patients with persistent LGD should undergo proctocolectomy^[69]. In contrast, several authors doubt the usefulness of LGD as a marker for UC-associated colorectal cancer. For example, some LGD lesions have been reported to disappear at close follow-up colonoscopy^[34]. Rosenstock *et al*^[13] reported that only 1 of 39 patients with LGD developed invasive carcinoma. Befrits *et al*^[70] reported that colectomy does not appear to be justified in patients with LGD in flat mucosa, even if it is repeated, as no progression to HGD was observed during 10 years of follow-up. Lim *et*

al^[71] stated that LGD diagnosis is not sufficiently reliable to justify prophylactic colectomy. Guidelines from the WHO recommend that repeat surveillance colonoscopy be performed at 3-6 mo in those with LGD, and that total proctocolectomy is advisable if dysplasia is multifocal, persistent, or shows DALM^[12].

Sporadic adenoma or dysplasia in patients with UC

As sporadic adenoma is not infrequent in the general population, incidental cases are also to be expected in patients with UC. Although the detection of sporadic adenoma on colonoscopy is feasible^[37,48], a problem is the difficulty in distinguishing this condition from dysplasia in biopsy specimens^[39,41]. In fact, several studies have treated both sporadic adenoma and dysplasia as definite dysplasia^[70,72]. Suzuki *et al*^[73] recommended taking several biopsy specimens from the surrounding flat mucosa. If specimens are negative for dysplasia, endoscopic polypectomy followed by close surveillance colonoscopy may be adequate. If positive, total proctocolectomy should be considered^[73]. Hata *et al*^[59] expected the pit pattern of the surrounding flat mucosa (not the lump itself) to distinguish sporadic adenoma from DALM. In cases of UC-associated dysplasia, the surrounding flat mucosa as well as the DALM itself showed Type III_L, IV pit pattern, indicating that the dysplasia had spread beyond the lump. With sporadic adenoma, the dysplastic pit pattern (Type III_L, IV) could be seen only on the surface of the lump, and the surrounding flat mucosa showed a normal pit pattern (type I), indicating that the dysplastic area was confined and thus that polypectomy was the treatment of choice. Rutter *et al*^[58] reported that small, well-circumscribed lesions detected after dye spraying were endoscopically resectable, and there has been growing evidence that a proportion of such lesions can be safely removed endoscopically without excess cancer risk^[74,75].

CONCLUSION

UC is a chronic inflammatory disease which shows repeated patterns of activity and remission in most patients. Magnifying colonoscopy is thought to be useful in the evaluation of disease activity and may be useful for predicting relapse in patients with UC. Patients with UC are known to be at increased risk of the development of colorectal cancer. Although its effectiveness has not been established in terms of cost and survival, surveillance colonoscopy should be performed for patients with long-standing UC until more effective methods are established. MCS is thought to be useful for the early detection and diagnosis of dysplasia and colorectal cancer. However, differentiation of dysplasia from epithelial regeneration is difficult both endoscopically and histopathologically. Novel tools are needed to improve the management of UC-associated colorectal cancer.

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