

MINI-REVIEW

Should we Sound the Alarm? Dysplasia and Colitis-associated Colorectal Cancer

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Abstract

Colorectal cancer is one of the most common malignancies and the most dreadful long-term complication in patients with ulcerative colitis. The incidence rate of colorectal cancer ranks second among the malignancies all over the world, and the number is still rising. Amid the many risk factors for colorectal cancer, ulcerative colitis is becoming increasingly prominent. The risk of colorectal cancer in ulcerative colitis patients is estimated to be as high as 40%. There is now a consensus that patients with long-lasting ulcerative colitis (>10 years) carries an increased risk of dysplasia and cancer. Taking into account evidence from the current studies, the longer ulcerative colitis lasts, the higher risk of colitis-associated colorectal cancer occurs. Unlike sporadic colorectal cancer, colitis-associated colorectal cancer usually derives from focal or multifocal dysplastic mucosa in areas of inflammation through an inflammation-dysplasia-carcinoma sequence. The prognosis of colorectal cancer is poorer in patients with ulcerative colitis than those without. Therefore the presence of dysplasia in ulcerative colitis patients is a critical indication of cancer that we should watch out for. Thus, early detection and resection of precursor lesions, mainly dysplasia, to terminate the cancerous progression is of great importance. To date, chemoprophylaxis, colonoscopy surveillance and proctocolectomy have been encouraged to prevent and manage dysplastic lesions in ulcerative colitis. This article attempts to give an overview of current research of dysplasia and prevention/management of dysplasia and colitis-associated colorectal cancer in ulcerative colitis.

Keywords: Colorectal cancer - ulcerative colitis - dysplasia - surveillance

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Introduction

Colorectal cancer (CRC) represents one of the most prevalent malignancies occurring worldwide that continues to cause a significant number of cancer-related deaths each year. Since CRC was first convinced as a dreadful complication of UC by Crohn and Rosenberger in 1925 (Crohn, 1925), many studies are carried out to substantiate the underlying relationship between ulcerative colitis (UC) and CRC (Ekbom et al., 1990; Eaden, 2004;

Jess et al., 2006; Chow et al., 2009; Kim et al., 2009). Patients with UC are 5 to 40 times more likely to develop CRC than general population. Risk of CRC for patients with ulcerative colitis is estimated to be 2% after 10 years, 8% after 20 years and 18% after 30 years of disease (Eaden et al., 2001).

The onset age of colitis associated colorectal cancer (CAC) is about ten years earlier than general population. Unlike sporadic CRC (detailed differences between them are shown in Table 1), CAC tends to have a longer clinical

Table 1. Differences between Colitis-Associated Colorectal Cancer and Sporadic Colorectal Cancer

	Sporadic	Colitis-Associated
Mean age of disease onset	about 60 years old	ten years earlier than sporadic CRC
Course of disease	vary greatly with many factors	associated with dysplasia, usually very long
Outcome of CRC	usually have a better prognosis	relatively bad prognosis
Lesion locations	mainly in sigmoid colon and rectum	may localize in every section of the colon
Lesion characteristics	single or multiple exophytic or invasive growth, with or without	most multiple, many in flat mucosa with unclear boundary invasive growth mainly low diff and mucous adenocarcinoma present in most of the patients
Dysplasia	adenoma-carcinoma sequence	inflammation-dysplasia-carcinoma sequence
Genetic sequence	LOH, MSI, CIMP	LOH, MSI, CIMP
Molecular changes	frequent early onset of k-ras and APC mutation and late changes of p53	DNA methylation and MSI early while LOH late early changes of p53 and late onset of APC

LOH, loss of heterozygosity; MSI, microsatellite instability; CIMP, CpG Island methylator phenotype

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course, which makes it hard to perform clinical research. However, the comparatively long interval also makes it possible for us to intervene the progression from UC to CRC. Most research indicate that a predominant majority of CAC are preceded by focal or multi focal dysplasia, which underlines the importance of timely detection and management of dysplasia lesions in UC. Early screening and proper management of dysplasia in UC decreases CAC incidence and mortality rates apparently. However, dysplasia takes on varied endoscopic appearances which complex the endoscopy surveillance. So there is a great need to improve the awareness of dysplasia and to develop diagnostic and management recommendations for patients with long lasting UC. In this review, we will discuss the prevention and management of dysplasia and CAC in UC patients.

Epidemiology of CAC

It has been widely accepted that UC is associated with increased rate of colorectal malignancy. According to a most accepted large meta-analysis carried out by Eaden and colleagues, the risk figure is 1.6% at ten years duration, 8.3% at 20 years and 18.4% at 30 years (Eaden et al., 2001). On the basis of this study, one in five UC patients would end up with CAC after thirty years of disease. Nevertheless, the figures vary in different regions around the world. The risk in Veszprem is 0.6% at 10 years, 5.4% at 20 years and 7.5% at 30 years (Lakatos et al., 2006), and the overall prevalence of CRC in UC patients is 0.37% in Korea (Kim et al., 2009), which are much lower than the previously data in Western European and North American. In Asia-Pacific, however, the incidence of CAC is relatively low but showing a steadily increase (Yang et al., 2000; Chow et al., 2009; Kim et al., 2009; Ooi et al., 2010). Nonetheless, in some regions, no increase or even a decrease in the incidence of CAC was observed (Winther et al., 2004; Jess et al., 2006; Lakatos et al., 2006). Some other studies have confirmed an increased risk of CAC in different countries, but the exact magnitude varies substantially (Ahmadi et al., 2009). These controversial data makes it difficult for us to tell whether there is an authentic change in the CAC incidence or it is merely a result of unidentified confounding factors. Viewing these literatures carefully, we can speculate that the disparity may arise from geographical variations, ethnic disparity and differences in research designs (Ahmadi et al., 2009; Winther et al., 2004). The discrepancy treatment and prevention measures of CAC can also make a difference (Leong and Koo, 2009). All in all, there is a trend of increased incidence of CAC in spite of some interpretable exceptions.

A multiple of studies have included the extent and duration of UC as the most important risk factors for CAC (Ekobom et al., 1990; Lakatos et al., 2006; Lakatos and Lakatos, 2008), and the risk increases in proportion to the duration and extent of disease. Others further indicate that the risk for CAC increases only in patients with extensive or total colitis rather than all the UC patients (Jess et al., 2006). The degree of colonic inflammation and dysplasia is associated with a higher risk of CRC (Rutter et al.,

2004; Gupta et al., 2007). Following the identification of concomitant primary sclerosing cholangitis (PSC) as a strong risk factor (Kornfeld et al., 1997; Vera et al., 2003; Loftus et al., 2005), some groups indicate that PSC and use of immune-suppressants were not statistically significant (Jess et al., 2006). There are still many risk factors under debate, including family history of CRC (Askling et al., 2001), early onset of UC, severity of inflammation, presence of black wash ileitis, medical therapy used (Lakatos and Lakatos, 2008; Leong and Koo, 2009) and frequency of exacerbations (Kim et al., 2009). Among these, 5-aminosalicylic acid (5-ASA) and ursodeoxycholic acid (UDCA) are beneficial in reducing CRC in UC patients (Lakatos and Lakatos, 2008; Leong and Koo, 2009). These controversial results may arise from differences in detection and management of CAC and the education level of objects.

Molecular Genetics of CAC

The exact mechanism by which UC escalate into CRC is still under study. To date, most of the current studies agree to the inflammation-dysplasia-carcinoma sequence as to the carcinogenesis of CAC. Meantime, it is well established that the main molecular changes occurring in sporadic CRC also present in CAC. These changes include Loss of Heterozygosity (LOH), Microsatellite Instability (MSI) and CpG Methylator Phenotype (CIMP) (Lakatos and Lakatos, 2008; Kulaylat and Dayton, 2010). Nonetheless, the frequency and timing of these changes in CAC are quite different from those in sporadic CRC. In CAC, DNA methylation and MSI tends to function at an early stage, while LOH appears to be a late event in carcinogenesis (Kulaylat and Dayton, 2010). In contrast to sporadic CRC, point mutations of the oncogen K-ras and tumor suppressor gene APC (Adenomatous Polyposis Coli) are less frequent. Additionally, inactivation of p53 by mutation and LOH is a common mechanism in CAC which occurs at a relatively early stage than sporadic CRC (Zisman and Rubin, 2008). Additionally, several groups demonstrate that CAC patients with precedent dysplasia tend to have an early onset of UC and a longer colitis-CRC interval (Brackmann et al., 2009). This result is quite dissimilar to our conventional conception. This may indicate the existence of an additional carcinogenesis for UC patients without dysplasia. In solving these issues, further studies are still needed.

Dysplasia and CAC

A majority of CAC originate in focal or multifocal dysplastic mucosa in areas of inflammation through an inflammation-dysplasia-cancer cascade. During UC, patients may present mucosa dysplasia and finally cancer as the duration of disease increases. The cancer begins either in the dysplastic mucosa or in the low villous projections (polyps). Historical subtypes of polyps in UC include inflammatory polyp, hyperplastic polyp and adenomatoid polyp, with the latter two carrying higher risk of developing into CRC. The term "dysplasia" refers to unequivocally neoplastic lesion occurring in the

epithelium (Zisman and Rubin, 2008). Morphologically, the appearances of dysplasia may be flat, raised or even depressed. We generally describe a sample as negative, indefinite, or positive, and the positive category can be further classified into two types: low grade dysplasia (LGD) and high grade dysplasia (HGD) (Riddell et al., 1983), with both of them carrying great risk of developing into cancer. Growing evidence demonstrates that the dysplasia is of higher grade and more extensive in UC patients with cancer than those without. And patients are at greater risk of cancer once dysplasia is found at colonoscopy (Bernstein et al., 1994; Gorfine et al., 2000). About as many as one third patients diagnosed with dysplasia are identified to have concurrent CRCs.

Dysplasia is reported to be a crucial independent risk factor (Brackmann et al., 2009; Kulaylat and Dayton, 2010) and a possible indication of colorectal malignancy, especially the multifocal ones. The presence of dysplasia is often associated with active inflammation, another risk factor for CAC (Taylor et al., 1992; Ullman et al., 2002; Rutter et al., 2004; Gupta et al., 2007). The widespread dysplasia in mucosa localized in or distant from the cancer occurs in 82% (Connell et al., 1994), 74% (Taylor et al., 1992) and 75% (Brackmann et al., 2009) patients at the diagnosis of CRC. That is to say, most of the CAC patients are complicated with concurrent dysplasia. Because these dysplasia lesions may also escalate into CRC, detection and management of the concurrent dysplasia should also be highly concerned about. In a study carried out by Lutgens et al. (2008) the diagnosis of CAC is missed or delayed in a substantial number of UC patients. There must be an under-estimate of CAC and dysplasia in the previous literatures due to technical limitation or disagreement between gastroenterologists, rather than inexistence of distal dysplasia in these patients. Thus, a thorough understanding of the definition and natural history of dysplasia are fundamental to the prevention and treatment of dysplasia preceding CRC.

Recently, a number of new names are raised to describe the lesions in CAC. Adenoma-like lesion or mass (ALM) represents the polypoid lesions resembling sporadic adenoma; and dysplasia associated lesion or mass (DALM) refers to elevated lesions visible but unable to resect under endoscopy. During the progression from UC to CAC, however, it is not necessarily for every patient to experience protruding lesions. Some of them just manifest flat or even depressed lesions that are difficult to detect and manage endoscopically. In these patients, carefully detection and management of dysplasia is an essential facet to interrupt the carcinogenesis of CAC is momentous.

Prevention/Management of Dysplasia and CRC in UC

Increasing evidence suggests that chemoprophylaxis, colonoscopy surveillance and surgical techniques for UC patients will allow for the identification of at-risk patients and the reduction of morbidity and mortality in these patients. Current recommendations for the prevention and early detection of dysplasia and CRC in the high

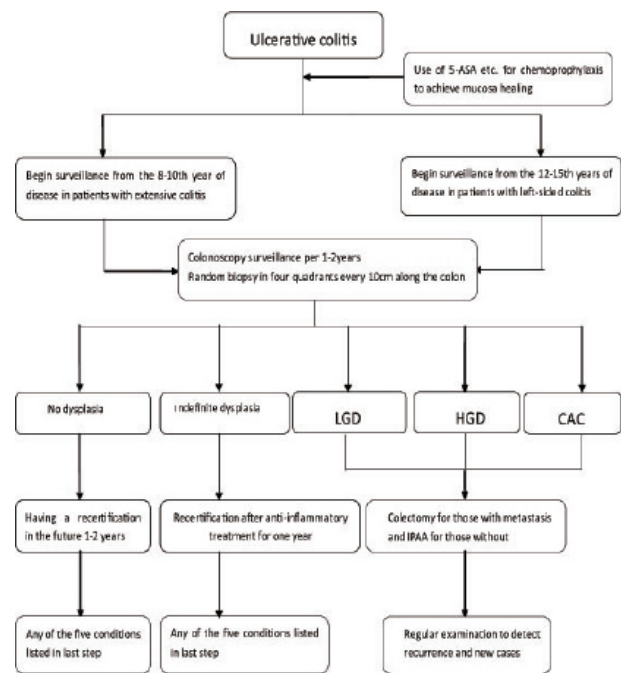


Figure 1. General Protocol for the Management of Colitis-Associated Colorectal Cancer

risk population are on the ground of the inflammation-dysplasia-carcinoma sequence. An understanding of the natural history of CAC, as well as the challenges associated with detection and interpretation of dysplasia are fundamental to developing an effective strategy for surveillance, prevention and management. The general protocol for management of CAC is shown briefly in Figure 1.

Chemoprophylaxis

According to current theory, inflammation is a main driving force of carcinoma in UC patients. Pharmacotherapy remains an essential treatment in UC patients to gain a symptomatic relief and better outcomes. However, the criteria before only includes improvement in symptoms as an endpoint of medication treatment, neglecting the importance of mucosa healing. Long-lasting non-healing mucosa inflammation may enhance the possibility of dysplasia and CRC in UC patients. A bad compliance of the patients and disagreement among gastroenterologists may account for the higher risk. Successful management of inflammation and dysplasia helps to prevent CAC. 5-aminosalicylic acid (5-ASA), which is the most widely studied agent for chemoprevention, is the first line medicine in the maintenance of remission in mild to moderate UC patients. 5-ASA, including mesalazine and sulfasalazine, may activate the peroxisome proliferator-activated receptor-gamma to exert their function as anti-inflammatory agent (Iacucci et al., 2010). In view of the anti-inflammatory function of 5-ASA, it can play a role in the chemoprophylaxis of dysplasia and cancer by achieving mucosa healing. Although there are sporadic reports about the uselessness of 5-ASA in prevention of CRC and dysplasia (Bernstein et al., 2003; Terdiman et al., 2007), a vast majority of studies are for the point that the use of 5-ASA compound is associated with a decreased risk of CAC (Velayos et al., 2005; Jess et al., 2007; Ooi

et al., 2010; Rubin et al., 2010). Considering the high tolerability of 5-ASA and its anti-inflammation function (Lichtenstein and Rutgeerts, 2010), the usage of 5-ASA as a chemoprevention medicine should be fully appreciated.

Another potential chemoprevention medicine is UDCA (Lakatos and Lakatos, 2008). Application of UDCA can reduce the rate of CRC development significantly (Pardi et al., 2003; Tung et al., 2001). However, no favorable study about UDCA in UC patients without PSC has been reported. Thus, we would better include the UDCA as a crucial part of treatment only in UC patients with PSC. Additionally, butyrate, which is effective in ameliorating the symptom of UC patients (Scheppach et al., 1992), is a potential candidate in chemoprevention. After butyric acid salt supplies treatment, reproduction rate of the intestinal crypts in the top returns to normal in active UC patients. This may greatly decrease the potential dysplastic lesion and ultimately CAC in UC. For the purpose of chemoprevention and management, many UC patients in clinical trials undergo barium enema or oral medication to gain an increase of butyrate concentration in the colon (Scheppach, 1996). Studies of the exact function of butyrate in chemoprevention are rare and deserve our further investigation. Other controversial medicines including corticosteroids, NSAIDs, folate, statins, calcium, and immunomodulators (Eaden et al., 2000; Itzkowitz and Harpaz, 2004; Matula et al., 2005) are still under discussion.

Colonoscopy surveillance

Recommendations for dysplasia and CRC surveillance in patients with long-standing UC are for the sake of detecting early neoplastic lesions at a curable stage and ultimately decreasing CRC incidence and mortality rate. A greater awareness of surveillance contributes to the decreasing incidence and longer survival of CAC in recent studies (Kim et al., 2009). The failure of colonoscopy surveillance in detecting CAC is probably owing to missed lesions/misdiagnose during the procedure, poor patients compliance, sampling error and lack of consensus regarding to the significance of dysplasia (Lim et al., 2003; Rutter et al., 2006). Another neglected cause for the failure may be the differences in availability of endoscopy in the distant and remote areas.

To date, colonoscopy surveillance has been included in guidelines for CAC prevention. According to a guideline, colonoscopy surveillance is recommended after 8–10 years diagnosis of extensive colitis and 12–15 years of left-sided colitis to determine the extent of the disease. And the interval of screening should decrease as disease duration increases, because the risk for CRC increases proportionally with time (Eaden and Mayberry, 2002). Others recommend regular surveillance and an increasing in screening interval from every three years in the second decade of disease to annually in the fourth decade. Biopsies should be taken during each colonoscopy and the results confirmed by at least two expert gastrointestinal pathologists (Eaden, 2004).

In the past few years, our techniques focus on random biopsies to identify dysplasia and early CAC, which are time-consuming and inefficient. Recent advances in the

new technologies for colonoscopy surveillance enhance the detection of dysplasia and early CACs remarkably (Hurlstone, 2008; Rutter et al., 2004; van den Broek et al., 2008). In addition to the traditional white light colonoscopy techniques, now we have chromoendoscopy, magnification endoscopy, narrow band imaging and confocal laser microscopy, which greatly enhance the efficiency of detecting precancerous lesion during surveillance. By using contrast dyes named indigo carmine and methylene blue, chromoendoscopy can visualize the mucosal changes in detail and improve the sensitivity and specificity of detecting possible lesions (Rutter et al., 2004), especially the flat and small lesions in chronic UC. However, the time of the total procedure is rather long than traditional techniques (Hurlstone, 2008). The confocal laser endomicroscopy can provide real-time histological evaluation of the mucosa, offering surface and subsurface cellular characterization in vivo in a relative short time, which reduces the time of procedure and the number of biopsy obviously. We can conduct in situ optical biopsies, determine the histology of suspicious lesions and map the extent of dysplasia during the confocal laser colonoscopy procedure. However, using this procedure, we are limited to the lamina propria. An increase of expenses and limitation of the examinable range are the main drawbacks of confocal laser endomicroscopy. Due to lack of prospective study with large sample, these techniques are not all fully used in clinical practice. We are deeply convinced that these techniques with individual advantages will play a vital role in the future. The clinicians will make choices between these procedures considering all the advantages and drawbacks to obtain an optimal outcome.

Surgery

Prophylactic colectomy in UC patients may bear the primary responsibility for the decreased CAC incidence (Leong and Koo, 2009). It is a curative treatment for those with precancerous dysplasia or early cancer as resected bowel obviously no longer has malignant potential. Presence of high grade dysplasia or extensive CIN (Colorectal Intraepithelial Neoplasia), which carry a high risk of synchronous or metachronous carcinoma are the absolute indications in UC patients. In the case of low grade dysplasia, however, the situation remains controversial. Some research demonstrate that low grade dysplasia is not sufficiently reliable to justify prophylactic colectomy (Lim et al., 2003; Jess et al., 2006), while others show that early colectomy should be recommended in UC patients with low grade dysplasia (Bernstein et al., 1994; Ullman et al., 2002; 2003). In view of the current research, we are in favor of early surgery for all the patients with dysplasia of any grade under the condition that the patients yield their consent after informed the gains and losses of colectomy.

The gold standard elective surgery for UC is proctocolectomy with ileal pouch anal anastomosis (IPAA) (Ooi et al., 2010). And possible complications of proctocolectomy include: minor to severe pouchitis, intestinal obstruction, and pelvic sepsis et al (Kulaylat and Dayton, 2010). What's more, people undergoing IPAA

may experience an impaired fecundity, so we should be cautious while making decisions (Stein and Michelassi, 2008). The final decision to operate should be made under the association of gastroenterologist, colorectal surgeon and patients. Additionally, the patients should also experience colonoscopy surveillance after operation in case of cancer developing in distal dysplastic lesions.

Conclusions

Most of the CAC undergoes an inflammation-dysplasia-carcinoma-sequence rather than the conventional adenoma-carcinoma sequence. Thus, great attention should be paid to dysplastic lesions in UC patients. Correct diagnose and assessment, proper surveillance, chemoprophylaxis and surgery constituent the overall management protocol of colorectal neoplasia in UC patients. Still pending are the protocol for application of novel endoscopic techniques and proper guidelines for surveillance. Close collaboration between the gastroenterologists and surgeon is needed while discussing the therapeutic schedule with UC patients to obtain a better outcome.

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