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TOPIC HIGHLIGHT

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Ulcerative colitis-associated colorectal cancer

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Abstract

The association between ulcerative colitis (UC) and colorectal cancer (CRC) has been acknowledged. One of the most serious and life threatening consequences of UC is the development of CRC (UC-CRC). UC-CRC patients are younger, more frequently have multiple cancerous lesions, and histologically show mucinous or signet ring cell carcinomas. The risk of CRC begins to increase 8 or 10 years after the diagnosis of UC. Risk factors for CRC with UC patients include young age at diagnosis, longer duration, greater anatomical extent of colonic involvement, the degree of inflammation, family history of CRC, and presence of primary sclerosing cholangitis. CRC on the ground of UC develop from non-dysplastic mucosa to indefinite dysplasia, low-grade dysplasia, high-grade dysplasia and finally to invasive adenocarcinoma. Colonoscopy surveillance programs are recommended to reduce the risk of CRC and mortality in UC. Genetic alterations might play a role in the development of UC-CRC. 5-aminosalicylates might represent a favorable therapeutic option for chemoprevention of CRC.

Key words: Ulcerative colitis-associated colorectal cancer; Risk factor; Dysplasia; Surveillance colonoscopy; Chemoprevention

Core tip: Colorectal cancer (CRC) is more frequent in patients with long-term ulcerative colitis (UC), and is one of the most serious and life threatening consequences of UC. Knowledge of risk factors for CRC is important to identify UC patients who need surveillance. Colonoscopy surveillance programs are recommended to reduce the risk of CRC and mortality in UC. Genetic alterations might play a role in the development of CRC in UC patients. 5-aminosalicylates might represent a favorable therapeutic option for chemoprevention of CRC.

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INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory bowel disease showing mucosal inflammation from the rectum to the oral side. Crohn and Rosenberg reported the first case of adenocarcinoma complicating UC in 1925[1]. The risk of developing colorectal cancer (CRC) is found to be high in patients with long-term UC[2,3]. UC-CRC is considered to develop from a non-neoplastic inflammatory epithelium to dysplasia to cancer. Therefore, colonoscopic surveillance in patients with long-standing UC has been recommended. UC-CRC shows characteristic clinicopathological features of CRC. In this paper, the characteristic properties of UC-CRC are reviewed.

CLINICAL FEATURES OF COLITIS-ASSOCIATED CRC

Clinicopathological features

UC-CRC patients are younger, more frequently have mul-

tiple cancerous lesions, and a macroscopically permeating pattern of spread, including mucinous or signet ring cell carcinomas, compared with sporadic CRC[1-3]. The advanced stage at presentation causes less favorable outcome of UC-CRC in IBD patients.

Incidence of UC-CRC

An inflammatory environment is believed to play an important role in the pathogenesis of UC-CRC in patients with chronic colitis[4]. UC-CRC accounts for about 1% of all CRC[5]. The risk of CRC begins to increase 8 or 10 years after the initial diagnosis[6-8]. Table 1 summarizes representative reports on the risk of developing colorectal cancer in patients with UC. Eaden *et al*[9] conducted a meta-analysis of 116 studies, and found that the probability of CRC in patients with UC increased with the duration of disease; 1.6% at 10 years after a onset of UC, 8.3% at 20 years after, and 18.4% at 30 years after. This increased incidence of UC-CRC is four to ten times greater than that for sporadic CRC, and the average age of onset is 20 years earlier. Several other studies reported that the risk of UC-CRC in UC patients was 5%-7% at 20 years after onset of disease[10-14], 7%-14% at 25 years[15,16] and 7.5%-18%[9,17] at 30 years. Eaden *et al*[9] confirmed that there is an increased risk for UC-CRC in pancolitis (5.4%), while the incidence in all patients with UC was 3.7%. In some countries, patients with UC have not been found to be at increased risk of CRC development. Winther *et al*[18] reported that the probability of CRC in Denmark was 0.4% by 10 years, 1.1% by 20 years, and 2.1% by 30 years of disease, suggesting that neither the overall cancer risk nor the UC-CRC risks increased after a median of 19 years of follow-up evaluation. This low rate of CRC development may reflect the high rates of surgical approach and chemoprevention for UC in Denmark. Taken together, the 5-aminosalicylic acid (5-ASA) treatment and frequent surveillance colonoscopy with proctocolectomy for dysplasia could explain the reduction in the incidence of CRC in UC patients. Moreover, current studies indicate that the risk of CRC seems to be lower. Rutter and coworkers reported cumulative incidences of UC-CRC of 2.5% at 20 years of colitis duration, 7.6% at 30 years, and 10.8% at 40 years[19] indicating only a 1.5 to 2-fold increased risk for CRC (5%) in comparison with the non-UC population. Söderlund *et al*[20] indicated that the overall cumulative incidence of CRC at 10, 20, and 30 years after the inflammatory bowel disease (IBD) diagnosis was 1%, 1.5%, and 2.7%, respectively. Manninen *et al*[21] reported only slightly increased risk for UC-CRC in UC patients in a Finnish cohort. Hata *et al*[22] reported that the cumulative risks for the development of invasive cancer at 10, 20, and 30 years were 0.5%, 4.1%, and 6.1%, respectively, while those for the development of definite dysplasia at 10, 20, and 30 years were 3.1%, 10.0%, and 15.6%, respectively. A further current systematic review with meta-analysis in 2014, based on 81 studies and 181923 patients, reported that the risk of UC patients developing colorectal cancer has decreased steadily, and the incidence rate decreased from 4.29/1000 patient-years in the 1950s to 1.21/1000 patient-years in the last decade[23]. The risk of developing CRC with longstanding Crohn's colitis is considered to be similar to that of UC, while the incidence of CRC in Crohn's disease showed various ranges in cancer risk[24-27].

Patients with UC who have undergone proctocolectomy have a very small risk of dysplasia in the ileal pouch[28]. Anal transitional zone dysplasia after ileal pouch-anal anastomosis is infrequent. Anal transitional zone preservation did not lead to the development of cancer in the anal transitional zone after five to ten years of follow-up[29].

Patients with UC who develop CRC have a worse prognosis than for CRC patients without UC[30-33], and the long-term prognosis of UC-CRC is even worse when patients with the same tumor stage are compared[32]. UC-CRC is frequently diagnosed at an advanced stage[33]. These findings emphasize the importance of knowledge of risk factor for UC-CRC and surveillance for patients with UC.

RISK FACTORS OF UC-CRC

Knowledge of risk factor for CRC is important to categorize subgroups of UC patients who need frequent surveillance or intense treatment. Risk factors for CRC in UC patients include, anatomical extent, young age at diagnosis, duration of disease, concurrent primary sclerosing cholangitis (PSC) and family history of CRC. In addition, smoking, pseudopolyps, persistent inflammation of the colon and backwash ileitis are also risk factor for CRC[34,35]. These UC patients with risk factors should be enrolled in an intensive surveillance program.

Pancolitis

The anatomical extent of colitis is an independent risk factor for the development of CRC. A meta-analysis showed that the incidence of CRC in patients with extensive UC was 5.4%[36]. Patients with pancolitis are at high risk of CRC, left-sided colitis is moderate risk, and proctitis and proctosigmoiditis are low risk, being similar to the non-UC population[20,37,38]. Ekbom *et al*[38] reported that UC patients with pancolitis had a 15-fold higher risk of CRC compared with the non-UC group, in contrast to an increased risk of 2.8 for patients with left-sided colitis and no significant increased risk for those with proctitis, and reported an overall risk of 4.8 for UC patients with extensive disease.

Young age

Young age at onset of colitis has been reported as an independent risk factor for CRC[6]. CRC risk varied by age at initial diagnosis of UC; patients diagnosed at childhood (0-19 years old) had a relative risk of 43.8 followed by those diagnosed in young (20-39 years old) with a relative risk of 2.65[39].

Table 1 Risk of developing colorectal cancer in patients with ulcerative colitis

Ref.	Year	Years after UC						Country
		10	15	20	25	30	40	
Gilat *et al*[14]	1988	0.2%	2.8%	5.5%		13.5%		Israel
Lennard-Jones *et al*[13]	1990		3%	5%				United Kingdom
Langholz *et al*[7]	1992				3.1%			Denmark
Eaden *et al*[9]	2001	1.6%		8.3%		18.4%		United Kingdom
Hata *et al*[22]	2003	0.5%		4.1%		6.1%		Japan
Winther *et al*[18]	2004	0.4%		1.1%		2.1%		Denmark
Lakatos *et al*[17]	2006	0.6%		5.4%		7.5%		Hungary
Rutter *et al*[107]	2006			2.5%		7.6%	10.8%	United Kingdom
Söderlund *et al*[20]	2009	1%		1.5%		2.7%		Sweden

UC: Ulcerative colitis.

Long disease duration

Duration of UC is an important risk factor for CRC development. Among patients with IBD, the median time from diagnosis of IBD to CRC was 17 years; 21% of IBD patients developed tumors within 10 years after onset[40].

PSC

IBD patients with PSC, a chronic cholestatic liver disease, have an increased risk of CRC[41]. Broomé *et al*[42] revealed a cumulative risk of CRC in UC patients with PSC of 9% after 10 years duration of symptoms, 31% after 20 years and as high as 50% after 25 years; compared with 2%, 5% and 10% in patients with UC alone matched for each duration. A meta-analysis found that 21% of UC patients with PSC developed CRC compared with 4% of UC patients without PSC. The risk of CRC in UC patients with PSC was 4.8-fold higher than that in patients with UC without PSC[43].

Family history of colorectal cancer

A family history of CRC in UC patients increases the risk of CRC, irrespectively of the type and extent of IBD, as compared with patients with UC without positive family history for CRC[44-46].

MOLECULAR FEATURES OF UC-CRC

Genetic characteristics detected in sporadic CRC, such as genetic mutations, microsatellite instability (MSI), and DNA hypermethylation, were also recognized in UC-CRC[4,33,47-50]. Mutations in *p53* occur early in the adenoma-carcinoma sequence and are often detected in non-dysplastic or indefinite dysplasia in UC, while *p53* mutations occur in the late phase in sporadic adenoma[51]. MSI is also relatively frequent in non-dysplastic inflamed epithelia, and transforming growth factor β receptor type II (*TGFβRII*) is one of genes targeted by the MSI process in UC-CRC[50]. Hyper-methylation of *hMLH1*[50,52], *p16INK4a*[53], and *p14ARF*[54] seems to precede dysplasia and contribute to the genetic alterations in UC-CRC[55]. MicroRNAs (miRNAs) play a critical role in regulating key pathogenic mechanism in IBD[56]. The miRNA-124a gene has a tumor-suppressive function and is methylated during carcinogenesis in UC patients, and the methylation level of miR-124a-3 is a promising marker for estimating individual risk for CAC[57]. By contrast, miRNA-155 overexpression is particularly associated with MSI in CA-CRC[58]. These molecules might be useful biomarkers for early detection and treatment response of CRC in IBD patients.

Inflammatory stresses, such as reactive oxygen species and some free radicals, may cause these genetic changes[59-61] and are considered to be factors in the pathogenesis of UC-CRC[62,63].

SURVEILLANCE COLONOSCOPY

Cancer surveillance is based on the high-risk factors that identify patients who are likely to develop cancer. The management of UC has changed with biological therapies, surgical treatment, and surveillance tools, which have reduced the risk of CRC in patients with UC[9,20,23]. Surveillance is recommended during the remission state to reduce the difficulty of differentiating reactive change from dysplasia[64]. Data from an 18-year surveillance program demonstrated that cancer was detected at an early stage in 80% of surveyed patients, compared with only 41% of non-surveyed UC patients[65]. There is evidence that surveillance colonoscopy reduces the risk of CRC and mortality in UC: The overall 5-year survival rate was 77% for the surveillance group, compared with only 36% for the control group[33,35,65]. It has been reported that a prior history of surveillance colonoscopy reduces the odds of developing CRC by 60%-80%[35,66].

These guidelines, commissioned by the Clinical Services' Committee of the British Society of Gastroenterology for clinicians and allied professionals caring for patients with IBD in the United Kingdom, provide an good clinical practice for surveillance and treatment[67]. The guidelines state that UC patients should be advised to have a review colonoscopy 8-10 years after disease onset to check the extent of colitis. Current recommendations are for regular surveillance every 1-2 years in the second decade of the disease to yearly by the fourth decade. The recommended guidelines for the surveillance of CRC in

Table 2 Timing of surveillance colonoscopy for colorectal cancer in ulcerative colitis

Ref.	Year	Guidelines	Beginning of surveillance (years after onset of symptoms)	Surveillance schedule
Van Assche *et al*[73]	2013	European Crohn's and Colitis Organization (ECCO)	8 yr	High risk[1]; 1-2 yr Low risk[1]; 3-4 yr
Farraye *et al*[72]	2010	American Gastroenterological Association (AGA)	8 yr	Extensive colitis or left-sided colitis; 1-2 yr Patients with PSC; 1 yr High-grade or low-grade dysplasia; colectomy or repeat colonoscopy within 6 mo Indefinite dysplasia; 3 to 12 mo No dysplasia; 1-2 yr
Kornbluth *et al*[70]	2010	American College of Gastroenterology (ACG)	8-10 yr	1-2 yr
Cairns *et al*[68]	2010	British Society of Gastroenterology (BSG)	10 yr	lower risk[2]; 5 yr intermediate risk[3]; 3 yr higher risk[4]; 1 yr
Leighton *et al*[69]	2006	American Society for Gastrointestinal Endoscopy (ASGE)	8-10 yr	1-2 yr (indefinite dysplasia: 3 to 6 mo)
Eaden *et al*[71]	2002	United Kingdom	8-10 years (pancolitis) 15-20 yr (left-sided colitis)	3 yr (second decade) 2 yr (third decade) 1 yr (fourth decade)

[1]Low-risk is 0-2 points and high-risk is 3-4 points; Risk factor: Pancolitis, endoscopic and/or histological inflammation, pseudopolyps, and family history of CRC: each risk factor is counted with one point; [2]lower risk: extensive colitis with no active inflammation or left-sided colitis; [3]intermediate risk: extensive colitis with mild active inflammation or post-inflammatory polyps or family history CRC in FDR aged ⩾ 50; [4]higher risk: active inflammation or stricture in past 5 years or dysplasia in past 5 years declining surgery or PSC/transplant for PSC or family history CRC in FDR aged < 50. PSC: Primary sclerosing cholangitis; CRC: Colorectal cancer; FDR: First-degree relatives.

UC by some societies[67-75] are summarized in the Table 2. These recommend surveillance programs are summarized as follows: (1) surveillance colonoscopy should be performed during remission state; (2) initial surveillance colonoscopy for CRC should be performed 8-10 years after onset; (3) regular surveillance should be performed annually or biannually; (4) surveillance colonoscopy for patients with PSC should be performed annually from the beginning of PSC diagnosis; (5) random biopsy of four lesions might be taken every 10 cm through the colon; and (6) if dysplasia is detected, the biopsies should be reviewed by a second gastrointestinal pathologist.

The main aim of surveillance programs is to detect dysplastic alterations. The cumulative probability of developing dysplasia or CRC in UC patients was 7.7% at 20 years and 15.8% at 30 years[13]. CRC incidence was 14 of 1000 UC patients-years' duration and the incidence of any advanced lesion was 30 of 1000 person-years' duration. When low-grade dysplasia (LGD) is detected on surveillance, there is a 9-fold risk of developing cancer and 12-fold risk of developing any advanced lesion[76]. Among patients with LGD who undergo colectomy, 19% will already harbor CRC or high-grade dysplasia (HGD) and 30%-50% will develop advanced neoplasia over the following 5 years[77-79]. HGD carries a 43% risk of synchronous cancer[80].

The guidelines described random biopsy[67]. A study of multiple biopsies taken at colonoscopy suggested that 33 biopsies are required to give a 95% chance of detecting dysplasia[81]. In contrast, targeted biopsies are recommended to increase the frequency of dysplasia detection, compared with random biopsies. Chromoendoscopy might improve the imagining of subtle mucosal changes that are suggestive of neoplasia, compared with standard endoscopy[82]. Indigo carmine contrast dye highlights irregularities in the mucosal architecture, improving the precision of endoscopic diagnosis. Methylene blue stains the normal epithelium of the colon; the absence of staining might indicate the presence of neoplastic changes in the intestine. Magnifying endoscopy could assist us to further visualize the delicate surface patterns[83].

On the other hand, some studies have highlighted the failures of surveillance colonoscopy by the guidelines[39,84,85]. In 50%-80% of cases with colitis-associated neoplasms, the lesions are not visible upon endoscopy[38]. It would be necessary to clarify that the surveillance systems could contribute to the decline of the mortality of UC patients.

TREATMENT FOR DYSPLASIA

Histopathological diagnosis of polypoid mucosa of UC is important with respect to clinical treatment for dysplasia. UC with HGD usually leads to a total colectomy because

of the high incidence of adenocarcinoma (42%-67% of the colectomy specimens)[75,79,86]. When HGD in flat mucosa is the initial discovery, surgery or polypectomy is done. Polypectomy should be performed along with biopsies taken from the surrounding mucosa. If the polypectomy is confirmed as complete and biopsies of the adjacent mucosa are negative for dysplasia, a follow-up examination within 6 mo should be performed[75,78]. If the dysplastic lesion persists or "dysplasia associated lesions or masses" (DALM) exists, a proctocolectomy should be performed[75].

In contrast, the management of LGD is controversial[87]. About 30%-50% of patients with LGD progressed to HGD or CRC; an unrecognized synchronous CRC may already be present in up to 20% of UC patients with LGD[77,79], which indicates that LGD is a risk factor for CRC. In contrast, some studies have shown that patients with LGD have a lower rate of CRC than previously reported[88].

Dysplasia found in DALM or in areas without any macroscopically visible mucosal alteration is believed to be the origin CRC[89,90]. The guidelines also state that particular attention should be paid to DALM that harbor a high risk of progression to CRC[71]. In addition, patients with DALM are recommended to undergo prophylactic proctocolectomy with an ileoanal pouch. By contrast, some polyps, such as adenoma-like mass (ALM), are unrelated to colitis and can be managed by endoscopic polypectomy because of less carcinogenic potential[91].

The serrated neoplasia pathway was recently proposed in CRC[92]. Serrated epithelial changes and sessile serrated polyps are uncommonly detected (0.2%-1%) by colonoscopy in chronic ulcerative colitis and Crohn's disease patients[93], while Bossard *et al*[94] found that serrated lesions, such as hyperplastic polyps and sessile serrated polyps/adenomas, accounted for approximately 7% of premalignant lesions in the inflamed mucosa of patients with IBD.

CHEMOPREVENTION

Chemoprevention refers to the use of an anti-inflammatory therapy or other substance to reduce or prevent the development of cancer. The current decreased incidence of CRC might be due to a better control of inflammation by improved medical therapy and higher rates of mucosal healing[95]. Intervening before the development of neoplasia might be promising method to decrease cancer and prevent colectomy.

5-ASA

5-ASA, the nuclear kappa-B pathway inhibitor, is a first line agent for anti-inflammatory therapy[96]. Continuing inflammation is a plausible mechanism causing malignant transformation; therefore, anti-inflammatory therapy might be useful for chemoprevention in UC patients. 5-ASA reduces oxidative stress, inhibits cell proliferation and promotes apoptosis[96]. Most reports indicated that 5-ASA reduces the risk of CRC in chronic ulcerative colitis[34,35,97,98]; however, a few did not. A meta-analysis performed by Herrinton *et al*[85] showed a protective association between the use of 5-ASA and CRC or a combined end point of CRC/dysplasia: in a pooled analysis of 334 CRC cases among patients with UC, regular use of 5-ASA reduced the risk of CRC by approximately 50%, similar to the regular use of nonsteroidal anti-inflammatory drugs (NSAIDs) in patients without UC[99]. In contrast, several studies did not find any chemopreventive effect of 5-ASA[100-102].

Ursodeoxycholic acid

Ursodeoxycholic acid (UDCA) may be a practical chemoprevention against colonic exposure to bile acid in patients with PSC[103]. UDCA use was closely associated with decreased prevalence of neoplasia because UDCA reduces the colonic concentration of the secondary bile acid as a carcinogen[104,105]. It has been reported that UDCA reduced the risk of CRC in PSC patients with IBD by 80%[103].

Steroids, aspirin, NSAIDs

There are several studies that suggest steroids, aspirin, and NSAIDs may reduce the incidence and mortality of CRC in UC[34,35,106].

Total colectomy

The cumulative CRC risk in patients with UC is 30%-40% at 20-30 years after onset of disease, which might suggest that total colectomy is recommend after 15 years of disease in patients with UC. However, the role for prophylactic colectomy in patients with IBD remains controversial.

FUTURE DIRECTION

Accumulating studies about UC-CRC suggest that control of long-term background inflammation and mucosal damage is vital. The use of maintenance chronic ulcerative colitis therapies could be an important strategy for reducing CRC risk in UC patients. Inflammatory stresses, such as reactive oxygen species and some free radicals, have been considered to cause genetic damages of UC epithelium. UC-CRC shows characteristic clinicopathological features. Analysis of the correlation between these genetic features and clinicopathological features might be useful to develop new therapies and to reduce the risk of UC-CRC in the future.

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