



Ulcerative colitis and colorectal cancer: Pathogenic insights and precision strategies for prevention and treatment

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Abstract

Ulcerative colitis (UC) is associated with an increased risk of developing colitis-associated colorectal cancer (caCRC), a major complication of long-standing disease. In this review, we examined the pathogenic association between UC and caCRC, highlighting the risk factors, molecular mechanisms, and current strategies for prevention and management. Compared to sporadic colorectal cancer, caCRC tends to occur at a younger age and is more frequently characterized by mucinous or signet-ring cell histology, proximal colonic involvement, and a higher incidence of synchronous lesions. The risk of caCRC increases 8-10 years after UC diagnosis and is influenced by disease duration, extent of colonic involvement, inflammatory burden, family history of colorectal cancer, and coexisting primary sclerosing cholangitis. The inflammation-to-cancer progression follows a multistep pathway of genetic alterations, advancing from low-grade to high-grade dysplasia, and ultimately to carcinoma. While chemopreventive agents such as 5-aminosalicylates may offer some benefit, surveillance colonoscopy remains the primary strategy for risk reduction. Early detection and individualized prevention strategies are critical for improving long-term

outcomes in patients with UC.

Key Words: Ulcerative colitis; Colorectal cancer; Prevention; Surveillance; Treatment

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Core Tip: Ulcerative colitis is a chronic inflammatory bowel disease with increased risk of colorectal cancer (CRC), particularly colitis-associated CRC (caCRC). The development of caCRC is influenced by disease duration, extent, severity, and factors such as primary sclerosing cholangitis and family history. Unlike sporadic CRC, caCRC tends to occur at a younger age and follows a distinct inflammation-dysplasia-carcinoma sequence. This review highlights the pathogenic link between ulcerative colitis and CRC and summarizes current strategies for prevention, surveillance, and management to improve patient outcomes.

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INTRODUCTION

Ulcerative colitis (UC) is an idiopathic inflammatory bowel disease (IBD) that typically begins in the rectum and extends proximally throughout the colon[1,2]. The global incidence and prevalence of IBD exhibit considerable geographic variation and temporal trends. Once considered a disease confined to Western industrialized nations, IBD is now rising rapidly in newly industrialized countries[3-5]. Recent data indicate that North America and Europe continue to have the highest prevalence, with rates exceeding 0.3% of the population, although the incidence in some regions is stabilizing or declining. In contrast, countries in Asia, the Middle East, and Latin America are experiencing a sharp increase in new UC cases, with incidence rates in parts of East Asia reaching 1.5-3 per 100000 person-years - an increase largely attributed to urbanization, Westernized dietary patterns, and improved diagnostic capabilities.

UC incidence is comparable between males and females, with most diagnoses occurring between ages 30 and 40[5]. An urban lifestyle, characterized by factors such as pollution, dietary changes, improved hygiene, reduced infections, and antibiotic use, is often implicated in colonic microbiome alterations and disruption of the intestinal mucosa, potentially influencing the UC disease course[6,7]. Abdominal pain, diarrhea, and hematochezia are the primary clinical features, although extraintestinal manifestations, including arthropathies and mucocutaneous or ophthalmic disorders, affect approximately one-third of patients[8,9]. Diagnosis relies on clinical evaluations, endoscopic findings, and histological confirmation[10]. First-line treatment includes 5-aminosalicylic acid (5-ASA), with or without corticosteroids and infliximab, to induce and maintain remission[11]. Intravenous corticosteroids and surgical intervention are reserved for patients with severe or nonresponsive UC[11].

Colorectal cancer (CRC) is among the most serious complications in patients with UC. Chronic inflammation (CI) of the colorectal mucosa is a well-established risk factor for CRC development. In UC, colitis-associated CRC (caCRC) arises due to multiple factors, including disease duration, extent of colonic involvement, persistent colitis from childhood, severity of the initial flare, coexisting primary sclerosing cholangitis (PSC), and a family history of CRC[1,2,4,5]. Compared to sporadic CRC (sCRC), caCRC typically presents at a younger age[12,13]. Its development follows a multistep pathway of accumulating genetic mutations, leading to aggressive mucosal changes from low-grade dysplasia (LGD) to high-grade dysplasia (HGD), and ultimately cancer. Although patients with UC have an elevated risk of CRC, the precise magnitude of this risk remains debated, owing to variations in study populations, methodologies, and the periods of published data [5,8-11,14,15]. Additional complexity arises from colonoscopic surveillance practices, medical therapies, and surgical interventions[16].

This review synthesizes current knowledge of the molecular, immunological, microbial, and histopathological mechanisms underlying caCRC. It also highlights recent advances in chemoprevention, risk stratification, surveillance, and surgical management. Framed in the context of precision medicine, this review provides a comprehensive and forward-looking overview that builds on and extends prior research in the field.

PATHOBIOLOGICAL BASES FOR caCRC AND PREMALIGNANT CONDITIONS

CRC arising in IBD exemplifies inflammation-induced carcinogenesis. CI promotes the release of reactive oxygen and nitrogen species, leading to oxidative stress-mediated deoxyribonucleic acid (DNA) damage and the accumulation of mutations in carcinogenesis-related genes[17]. Beyond mutagenesis, CI triggers epigenetic changes, alters epithelial

turnover, disrupts the intestinal barrier, and modifies gut microbiota (GM) composition. The host immune response further perpetuates this cycle, driving the inflammation-dysplasia-carcinoma sequence characteristic of caCRC[18,19].

Molecular and cellular mechanisms

CI contributes to carcinogenesis through two mechanisms: A direct pathway involving oxidative stress and DNA damage and an indirect pathway mediated by cytokines produced by inflammatory and intestinal epithelial cells[19-22]. In IBD, dysregulated immune responses promote the release of proinflammatory cytokines[21], notably interleukin (IL)-6, which activates the Janus kinase/signal transducer and activator of transcription 3 (STAT3) pathway[23-25]. This signaling pathway enhances epithelial cell proliferation and impairs apoptosis, thereby fostering a tumor-promoting environment [24,25].

Additional mediators, such as nuclear factor kappa B and suppressor of cytokine signaling 3, interact with STAT3 to sustain inflammation and drive carcinogenesis[25-32]. While anti-inflammatory cytokines such as transforming growth factor-beta exert protective effects in early disease, they might become dysregulated or inactive in later stages due to mutations[33-35]. Other signaling pathways, including the apoptosis signal-regulating kinase 1/mitogen-activated protein kinase cascade, further contribute to tumor progression by modulating cell survival and innate immune functions [36].

Immune cells, such as tumor-infiltrating leukocytes and tumor-associated macrophages, and immune proteins such as S100a9 might play a significant role in CI and carcinogenesis, serving as prognostic biomarkers and therapeutic targets for anticancer therapy[37-39]. However, clinical evidence supporting these roles remains lacking, and further investigation is warranted. In addition to the canonical IL-6/STAT3 and nuclear factor kappa B pathways, several other molecular alterations have been identified in caCRC. Epigenetic modifications, such as promoter hypermethylation, histone modifications, and dysregulated micro-ribonucleic acid (microRNA) expression, contribute to tumor initiation and progression by silencing tumor suppressor genes and impairing immune surveillance[40]. Dysregulation of Wnt/ β -catenin signaling and cellular-MYC amplification has also been implicated, particularly in mucinous and signet-ring cell subtypes of caCRC[41]. These cumulative genetic and epigenetic alterations highlight the molecular heterogeneity of caCRC and represent promising targets for individualized therapeutic strategies. Table 1 summarizes the key molecular and cellular pathways implicated in caCRC.

Histological features

Unlike sCRC, caCRC develops from dysplastic lesions affecting extensive areas of chronically inflamed mucosa[42]. The diagnosis of dysplasia (intraepithelial neoplasia) relies on cytohistological criteria and is currently classified into LGD and HGD using the Riddell or Vienna system[43]. Given the limited interobserver agreement, any biopsy indicating dysplasia should be confirmed by an experienced gastrointestinal pathologist. Dysplasia in UC is often multifocal, and early neoplastic changes might be inconspicuous on colonoscopy because they could be flat and resemble inflamed mucosa[44, 45]. However, dysplastic lesions may appear as elevated masses, dysplasia-associated lesions or masses, resembling pedunculated polyps or velvety plaques, similar to sporadic adenomatous or villous polyps, respectively[46].

IBD-associated dysplasia functions not only as a precursor but also as a potential marker of concurrent cancer[47]. The progression from early dysplasia to CRC involves a series of molecular alterations shared with sCRC and caCRC, though with distinct timing and frequency (Figure 1). More recently, non-conventional lesions resembling those found in hyperplastic/serrated polyposis syndrome have been identified in patients with IBD with long-standing disease. These findings suggest the presence of a serrated pathway of carcinogenesis in IBD, involving O(6)-methylguanine DNA methyltransferase silencing, likely due to promoter hypermethylation and Kirsten rat sarcoma viral oncogene homolog mutations[48].

Immunological influences

Immune cell subsets, particularly cluster of differentiation 4+ T helper (Th) cells, play a pivotal role in caCRC pathogenesis. Proinflammatory Th17-associated cytokines, including IL-9, IL-17, and IL-22, reportedly promote dysplasia and neoplasia in murine models and human tissues[46-49].

Macrophages exhibit dual roles, with M1 macrophages exerting anti-tumoral effects and M2 macrophages facilitating tumor progression and metastasis through IL-13 production and chemokines such as chemokine ligand 17[50-55]. Recently, Kvorjak *et al*[56] identified a novel regulatory axis between macrophages and colonic cells in UC and caCRC. Their study demonstrated that chemokine ligand 17 and IL-13 secreted by M2 macrophages co-cultured with colon cells activated oncogenic signaling pathways, including protein kinase B and STAT6. These cytokines also induced aberrant ST6GALNAC1 glycosyltransferase overexpression, resulting in elevated expression of the tumor glycoform mucin1, cell surface associated with sialylated Thomsen-nouvelle antigen, which has been implicated in tumor progression, metastasis, and immune modulation[57].

Innate lymphoid cells and regulatory T cells (Tregs) contribute to local immune homeostasis; however, their roles in tumor regulation are context-dependent and subject to ongoing debate. Innate lymphoid cells maintain intestinal homeostasis by promoting protective immune responses, yet they are also implicated in IBD pathogenesis and cancer progression in caCRC[58]. Similarly, Tregs, which are key regulators of tissue inflammation and autoimmunity, exhibit a complex role in sCRC and caCRC[59]. While some studies have reported a positive correlation between high Treg infiltration and improved control, others have failed to replicate these findings[60]. Overall, current evidence favors an antitumorogenic function of Tregs in sCRC and caCRC[61,62].

Table 1 Summary of key molecular and cellular pathways in colitis-associated colorectal cancer

Pathway/cell type	Key mediators	Biological role	Impact on tumorigenesis
IL-6/JAK/STAT3 pathway	IL-6, JAK, STAT3	Promotes epithelial proliferation and inhibits apoptosis	Facilitates CI and epithelial transformation
NF-κB signaling	NF-κB, TNF-α	Controls immune and inflammatory gene expression	Sustains pro-tumorigenic inflammation
TGF-β pathway	TGF-β, TGFBR2	Regulates epithelial growth; normally anti-proliferative	Loss or mutation promotes tumor progression
SOCS3 regulation	SOCS3	Inhibits STAT3-mediated signaling	Dysregulation leads to enhanced inflammation and carcinogenesis
MAPK/ASK1 signaling	ASK1	Mediates stress response and immune modulation	ASK1 deficiency exacerbates inflammation and susceptibility to cancer
CD4+ T helper cells	IL-17, IL-22, IL-9	Stimulate epithelial regeneration and immune activation	Promote dysplasia and tumor development
Macrophages (M1/M2)	IL-13, CCL17 (M2), TNF-α (M1)	M1: Antitumor; M2: Tumor-promoting <i>via</i> immunosuppression and cytokine release	High M2 infiltration is linked to poor prognosis and metastasis
Regulatory T cells	FOXP3, IL-10	Maintain immune tolerance and suppress inflammation	Dual role: Contextually antitumor or tumor-permissive
Tumor-infiltrating leukocytes	Various cytokines and chemokines	Orchestrate local immune response	Serve as prognostic markers; role depends on cellular composition
S100 family proteins	S100A9, S100A8	Mediate inflammation and immune cell recruitment	Correlated with tumor progression; potential therapeutic targeting

IL: Interleukin; JAK: Janus kinase; STAT: Signal transducer and activator of transcription; CI: Chronic inflammation; NF-κB: Nuclear factor kappa B; TNF: Tumor necrosis factor; TGF-β: Tumor growth factor-beta; TGFBR2: Transforming growth factor beta receptor 2; SOCS: Suppressor of cytokine signaling; MAPK: Mitogen-activated protein kinase; ASK: Apoptosis signal-regulating kinase; CCL: Chemokine ligand; FOXP3: Forkhead box P3.

Microbiota and metabolites

Growing evidence indicates that GM plays a crucial role in sCRC and caCRC development[63]. However, whether carcinogenesis in the context of CI is driven by specific microbial species or by broader shifts in microbiota composition remains unclear. Comparative analyses have not identified any significant differences in microbiota composition between healthy individuals and patients with sCRC and caCRC. Nevertheless, caCRC is generally associated with a reduced abundance of *Bacteroidetes* and *Firmicutes*, and an increased prevalence of *Proteobacteria*, whereas sCRC is characterized by reduced *Bacteroidetes* and a marked expansion of *Fusobacteria*[64].

The tumorigenic potential of specific microorganisms is well-established in the case of *Fusobacterium nucleatum* in sCRC, where high bacterial loads correlate with enhanced tumor growth, distant metastasis, and poor prognosis[64]. Recent studies have also implicated *Fusobacterium nucleatum* in exacerbating tumorigenesis in a caCRC mouse model by activating the epidermal growth factor receptor signaling pathway and induction of epithelial-to-mesenchymal transition [65].

Enterobacteriaceae/Escherichia coli (*E. coli*) strains harboring the *pks* gene cluster have been detected more frequently in patients with IBD and CRC than in healthy individuals[66]. Certain strains, such as *pks+* *E. coli*, are associated with oncogenic phenotypes and promote tumor formation in murine models of caCRC[67]. However, the role of *pks+* *E. coli* in human caCRC pathogenesis remains to be fully elucidated.

Enterotoxigenic *Bacteroides fragilis* (*B. fragilis*) secretes *B. fragilis* toxin (BFT), which has been linked to diarrheal disease, IBD, and CRC. BFT directly interacts with epithelial cell receptors, inducing cell proliferation, proinflammatory mediator release, and DNA damage[68]. Inflammatory conditions characterized by a Th17 response might amplify this effect through BFT-induced STAT3 activation in epithelial and mucosal immune cells, thereby promoting tumorigenesis[69,70]. In contrast, animal studies suggest that non-toxigenic *B. fragilis*, also present in healthy GM, might exert protective effects against colitis and polyp formation[71].

Additionally, GM influences CI and tumor development through its metabolic byproducts. Among these, short-chain fatty acids, such as propionate, butyrate, and acetate, are abundant in starch-rich diets and have demonstrated anti-inflammatory effects in UC. Short-chain fatty acids regulate epithelial cell proliferation and induce apoptosis; their exogenous administration lowers IL-6, tumor necrosis factor-α, and IL-17A expression and reduces tumor cell proliferation in caCRC models[72]. Metabolomic analysis of the intestinal microbiota may enhance our understanding of its role in colonic carcinogenesis and aid in caCRC prevention.

Sporadic and colitis-associated CRC progression

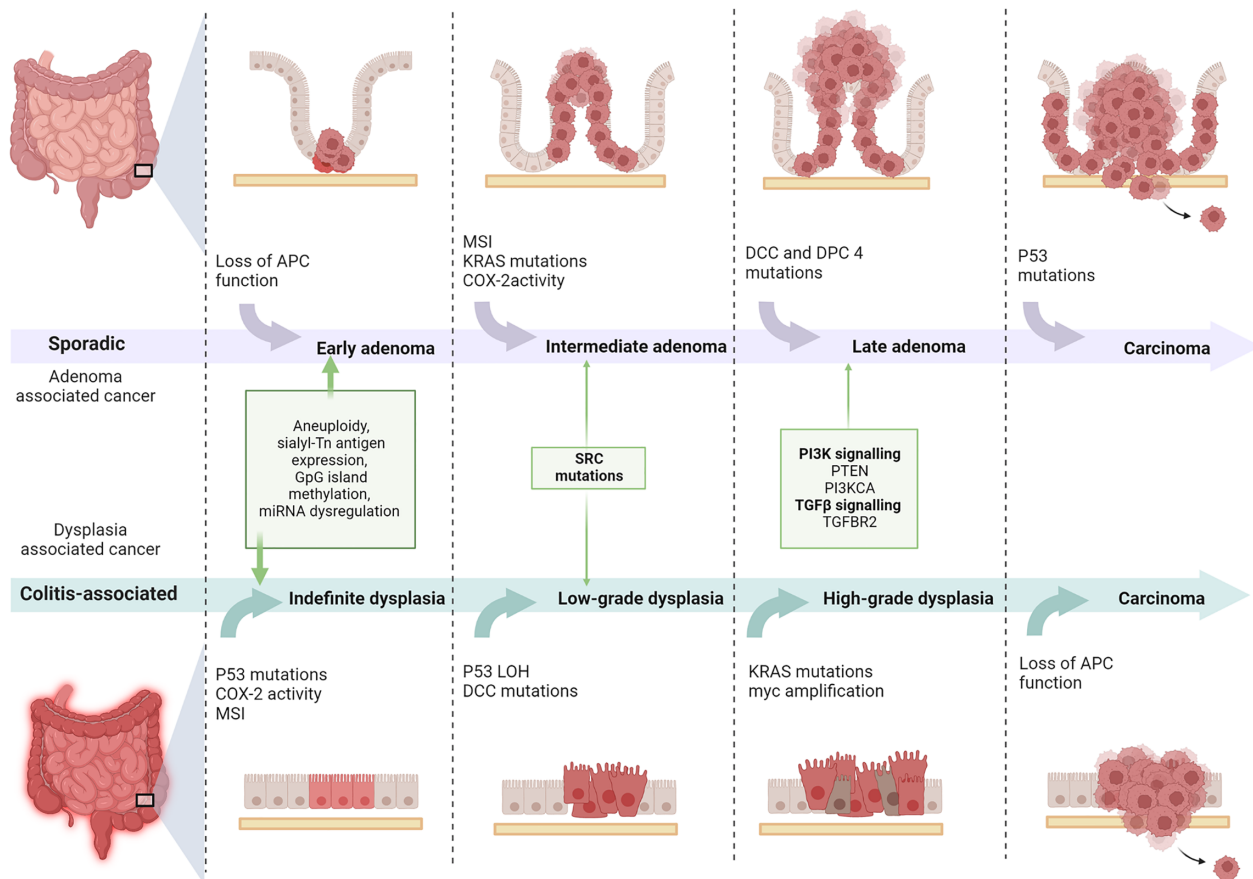


Figure 1 Colorectal cancer progression and overexpression of stage-specific markers. Above: Sporadic colorectal cancer characterized by the adenoma-carcinoma sequence. Below: Colitis-associated colorectal cancer characterized by the inflammation-dysplasia-carcinoma sequence. The two sequences differ in the overexpression of several markers, varying in frequency and timing. Image created with BioRender.com. CRC: Colorectal cancer; APC: Adenomatous polyposis coli; MSI: Microsatellite instability; COX-2: Cyclooxygenase-2; DCC: Deleted in colorectal cancer; PTEN: Phosphatase and tensin homolog; PI3KCA: Class A phosphoinositide 3-kinases; TGF: Transforming growth factor; TGFBR2: Transforming growth factor beta receptor 2.

CHEMOPROPHYL AXIS, SCREENING, AND SURVEILLANCE STRATEGIES

Several chemopreventive agents, including 5-ASA, thiopurines, and biologic therapies, have demonstrated potential in reducing CRC risk. However, the current evidence remains inconclusive, and further investigation is warranted[73]. Table 2 summarizes the preventive effects of these agents on caCRC. In contrast to the adenoma-carcinoma sequence characteristic of sCRC, caCRC typically progresses through an inflammation-dysplasia-carcinoma pathway. Therefore, regular surveillance of patients with IBD is essential for the early detection of dysplasia and cancer[74]. Evidence suggests that surveillance colonoscopy reduces CRC incidence and mortality in UC[75,76]. The recently updated guidelines from the American Gastroenterological Association recommended initiating endoscopic screening for caCRC 8 years after symptom onset rather than the date of diagnosis[77]. Surveillance intervals should be individualized based on risk factors such as age at diagnosis, disease duration, active endoscopic or histological inflammation, family history of CRC, and the presence of pseudopolyps[78-85]. Patients with concomitant PSC are at a higher risk and should begin annual screening from the time of PSC diagnosis[86,87]. The British Society of Gastroenterology and the European Crohn's and Colitis Organization (ECCO) stratify patients into low-, intermediate-, and high-risk groups, with recommended surveillance intervals ranging from 1 to 5 years[88,89]. Similarly, the American Society for Gastrointestinal Endoscopy recommends extending surveillance intervals following two consecutive colonoscopies without endoscopic or histological abnormalities[90]. Surveillance strategies proposed by ECCO, American Gastroenterological Association, and the American College of Gastroenterology are presented in Table 3.

Colonoscopy remains the cornerstone of secondary prevention of CRC in UC, while novel endoscopic techniques have been developed to enhance dysplasia detection (Table 4). Tumor-associated biomarkers, such as aneuploidy, tumor protein p53 mutations, DNA methylation patterns, and microRNA profiles, have been identified in caCRC[91,92]. The evaluation of these biomarkers in colorectal biopsies and other biospecimens (*e.g.*, blood, stool, and urine) offers a promising approach for monitoring carcinogenic progression in UC. Although the clinical utility of these biomarkers requires validation in larger prospective studies, molecular testing is expected to significantly advance the development of high-performance diagnostic and screening tools in the future.

Table 2 Chemopreventive drugs in colitis-associated colorectal cancer

Compound	Reported effect	Recommendation	Ref.
5-ASA	Protective effect for patients with long-standing extensive colitis. Lower risk of developing CRC/dysplasia in UC patients	Mesalamine compounds have a recognized protective role against CRC in UC patients	[99-101]
Thiopurines	Protective against HGD and CRC risk in IBD patients	No recommendations due to their carcinogenic effects (<i>i.e.</i> , lymphoma, urinary tract cancer, non-melanoma skin cancer)	[102-104]
Biologic drugs	Chemopreventive effects of anti-TNF- α treatment in IBD patients	No recommendations	[101,105-107]
Statins and folic acid	Controversial chemopreventive role of statins on CRC in IBD patients. Protective effects of folate supplementation against CRC development	No recommendations	[108-110]
UDCA	Decrease in colonic dysplasia in patients with UC and PSC. Chemopreventive effects on risk of advanced CRC and HGD	No recommendations	[111]
NSAIDs and aspirin	No significant chemoprotective role in CRC risk	No recommendations	[112]

ASA: Aminosalicylic acid; CRC: Colorectal cancer; UC: Ulcerative colitis; IBD: Inflammatory bowel disease; HGD: High-grade dysplasia; TNF: Tumor necrosis factor; UDCA: Ursodeoxycholic acid; PSC: Primary sclerosing cholangitis; NSAIDs: Nonsteroidal anti-inflammatory drugs.

Table 3 Endoscopic surveillance strategies in inflammatory bowel disease

Frequency of surveillance		
ECCO 2017	Every year (high risk)	PSC or stricture or dysplasia detected within past 5 years or extensive colitis with severe active inflammation or family history of CRC in FDR age < 50
	Every 2-3 years	Extensive colitis with mild or moderate active inflammation or post-inflammatory polyps or family history of CRC in FDR age > 50
	Every 5 years	Absence of intermediate or high-risk features
ACG 2019	Every year	PSC
	Every 1-3 years	UC of any extent beyond the rectum
	Adjust intervals	Based on previous colonoscopies and combined risk factors: Duration of disease, younger age at diagnosis, greater extent of inflammation, FDR with CRC
AGA 2021	Every year	Moderate or severe inflammation (any extent), PSC, family history of CRC in FDR age < 50, dense pseudopolypoidosis, history of higher-risk visible dysplasia < 5 years ago
	Every 2-3 years	Mild inflammation (any extent), strong family history of CRC (but no FDR age < 50), features of prior severe colitis (moderate pseudopolyps, extensive mucosal scarring), history of invisible dysplasia or higher-risk visible dysplasia > 5 years ago, history of lower risk visible dysplasia < 5 years ago
	Every 5 years	Continuous disease remission since last colonoscopy with mucosal healing on current exam, plus either of: ≥ 2 consecutive exams without dysplasia, minimal historical colitis extent (ulcerative proctitis or < 1/3 of colon in CD)

ECCO: European Crohn's and Colitis Organisation; ACG: American College of Gastroenterology; AGA: American Gastroenterological Association; PSC: Primary sclerosing cholangitis; CRC: Colorectal cancer; FDR: First degree relative; UC: Ulcerative colitis; CD: Crohn's disease.

SURGICAL MANAGEMENT OF DYSPLASIA AND CANCER

The detection of dysplasia during colonoscopy prompts a critical decision between continued surveillance and surgical intervention[82,83]. Non-polypoid dysplasia, regardless of grade, and endoscopically occult HGD, including flat, random, or non-targeted lesions, are associated with a high risk of synchronous and metachronous carcinoma. Consequently, prompt colectomy is generally recommended for patients with these lesions[84,85]. In contrast, the management of endoscopically invisible LGD remains controversial due to conflicting data regarding its association with synchronous CRC and its progression to HGD and/or CRC[93-101]. A meta-analysis by Thomas *et al*[6] estimated a 22% positive predictive value for concurrent CRC at colectomy in patients with flat LGD. LGD detected during surveillance was associated with a nine-fold increased risk of progression to CRC and a 12-fold increased risk of developing advanced neoplasia (HGD and CRC). A more recent meta-analysis revealed that synchronous CRC was present in approximately 17% of surgical cases. Among patients with UC-associated LGD under surveillance, the annual progression rate to CRC and advanced neoplasia was 0.8% and 1.8%, respectively[102]. Given these risks, prophylactic proctocolectomy should be

Table 4 Current available endoscopic procedures for colitis-associated colorectal cancer surveillance

Type of procedure	Type of biopsies	Strengths	Limitations
Standard with light endoscopy	Random biopsies	Increases dysplasia detection rate	Longer procedure times and cost
High-definition endoscopy	Targeted biopsies	Images of substantially higher resolution for dysplasia detection	Cost
Chromoendoscopy	Targeted biopsies	Best at highlighting irregularities in the architecture of the mucosa thanks to the contrasting dye	Specialized equipment and additional training required, longer procedure time
Narrow band imaging	NA	Greater contrast of the mucosal surface	Lower sensitivity in dysplasia detection
Fujinon intelligent color enhancement and I scan digital contrast	NA	Perception of subtle changes of the mucosal surface	Limited relevant data
Confocal laser endomicroscopy	NA	Real-time microscopy available <i>in vivo</i> during examination	Longer procedure time, extra equipment and training required
Full-spectrum endoscopy	NA	Better visualization of the mucosa thanks to increased visual field	Longer withdrawal and total procedure time

NA: Not available.

offered as an alternative to continued surveillance for patients with LGD in flat mucosa[103].

Given the multifocality and potential for recurrence of neoplastic lesions, partial colectomy is generally considered unsuitable; however, it might be selectively considered in elderly patients[104,105]. Subtotal colectomy with ileorectal anastomosis also poses limitations, as the presence of colonic carcinoma or dysplasia at the time of surgery significantly increases the risk of malignancy in the retained rectal stump[106]. Proctocolectomy is widely accepted as the preferred surgical approach for caCRC; however, the optimal reconstruction method - definitive end ileostomy *vs* restorative proctocolectomy (RPC) - remains a subject of debate.

Over the past decades, RPC with ileal pouch-anal anastomosis (IPAA) has been increasingly adopted in UC-associated neoplasia. Functional outcomes following IPAA are generally favorable and comparable to those achieved in patients undergoing IPAA for non-neoplastic UC[107,108]. However, the pouch failure rate in patients with UC and CRC is significantly higher than in those without CRC, ranging from 14.2% to 19%[109]. In cases where caCRC involves the rectum, the success of IPAA is largely dependent on tumor stage, with reported failure rates of 16%-28% in locally advanced cancers[110,111]. In contrast to sCRC, where preoperative radiotherapy (RT) or chemoradiotherapy is standard for T3-4 or node-positive tumors of the middle and lower rectum, these modalities are rarely employed in patients with UC and rectal cancer. Current ECCO guidelines recommend RT before pouch surgery and avoiding it after IPAA due to the associated complication risk[103].

The potential for IPAA to increase the risk of pouch dysplasia and carcinoma in patients with caCRC remains debatable. A comprehensive review by Das *et al*[98] identified 17 confirmed cases of adenocarcinoma arising in the ileal pouch or anorectal mucosa, with most tumors originating from residual rectal mucosa in the anal transitional zone (ATZ). Notably, the interval between RPC and cancer diagnosis generally exceeded 2 years[112]. In a separate study with a median follow-up of 12.9 years, Mark-Christensen *et al*[99] reported only two cases of pouch carcinoma among 1723 patients with UC who underwent IPAA. Long-term data from large population-based studies conducted by the Cleveland Clinic and the Dutch Pathology Registry estimated the cumulative incidence of pouch neoplasia, including adenocarcinoma, lymphoma, squamous cell carcinoma, and dysplasia, at 5.1% over 25 years and 6.9% over 20 years, respectively[99,100].

PSC represents an additional risk factor for pouch malignancy. Patients with PSC and UC might develop CRC either in the residual colon following subtotal colectomy and ileorectal anastomosis or in the ileal pouch following IPAA[113,114]. In a cohort of 65 patients who underwent IPAA for refractory colitis (40%), dysplasia (48%), or carcinoma (10.8%), Imam *et al*[115] reported a 5-year cumulative incidence of pouch neoplasia of 5.6%.

An ongoing area of debate concerns whether the type of pouch anastomosis - handsewn at the pectinate line following mucosectomy of the rectal mucosa of the anal canal *vs* stapled at the level of the distal rectal mucosa - affects the risk of ATZ cancer[116]. Several studies have reported comparable rates of dysplasia and cancer between the two techniques [107,114]. Dysplasia in the ATZ is typically managed through mucosectomy or regular check-ups, depending on the number of positive biopsies and the severity of dysplasia detected[117]. Notably, ATZ neoplasia might originate from pre-existing dysplasia in the rectal mucosa at the time of IPAA[112]. Mucosectomy is generally recommended when dysplasia or cancer is identified in the distal rectum, whereas rigorous endoscopic surveillance with targeted biopsies of the ATZ is advised if mucosectomy is not performed[118,119].

Squamous cell carcinoma after IPAA is exceedingly rare. In a systematic review, Pellino *et al*[104] identified eight cases of IPAA-related squamous cell carcinoma, six involving the ATZ or rectal cuff and two arising within the pouch body. Notably, no recurrence or disease progression was observed after ATZ mucosectomy with redo-IPAA, suggesting that surgical excision of the ATZ might preserve pouch function while reducing the risk of squamous neoplasia.

TREATMENT COURSE AND OUTCOME

Conflicting data exist regarding the prognosis of patients with UC and CRC. While several studies have not identified any significant differences in survival between patients with caCRC and those with sCRC[110,120-124], others have revealed a higher mortality risk in patients with caCRC[120,125,126]. Watanabe *et al*[109] observed poor overall survival in patients with UC and stage III tumors but found no difference in overall and cancer-specific survival when all cancer stages were considered. In a study by Olén *et al*[110], patients with UC and a disease duration of ≥ 8 years or a diagnosis of PSC demonstrated an increased risk of CRC-related mortality compared to matched controls, despite presenting with tumors at an earlier stage.

The poor prognosis reported in some caCRC cases might reflect distinct clinico-histological and molecular characteristics compared to sCRC. Mucinous and signet-ring cell carcinomas, which are more prevalent in caCRC, are often diagnosed at advanced stages and carry a higher risk of recurrence[127,128]. These mucin-producing tumors are also less responsive to standard chemotherapy, potentially due to a higher prevalence of microsatellite instability (MSI)[129,130]. Notably, although CRCs in UC share histological features with sporadic MSI-high and Lynch syndrome-associated CRCs, such as mucinous and signet-ring differentiation, they are predominantly microsatellite stable. One hypothesis suggests that inflammation-induced overexpression of microRNAs targeting mismatch repair proteins might serve as an early event in the development of MSI in IBD-associated carcinogenesis. Further research is needed to elucidate the molecular mechanisms underlying the clinical behavior in IBD-associated CRC.

In recent years, the incidence of early-stage caCRC has increased. Contemporary literature reports that 50%-60% of newly diagnosed caCRCs are classified as stage I or II. This shift is likely attributable to increased awareness of cancer risk among patients with UC, along with the implementation of more effective and timely surveillance strategies that promote patient compliance.

CONCLUSION

CRC remains a significant clinical concern in patients with UC, particularly among those with long-standing disease, elevated inflammatory burden, concomitant PSC, or a history of dysplasia. CI is the principal driver of caCRC, and although its molecular alterations overlap with those in sCRC, their sequence and frequency differ in the inflammatory context. Current surveillance strategies based on colonoscopic monitoring and lesion resection have reduced CRC-related morbidity and mortality in UC. However, the occurrence of interval cancers highlights the limitations of uniform surveillance protocols. To improve clinical outcomes, surveillance paradigms must transition toward risk-adapted strategies guided by molecular and histological biomarkers. Future research should focus on integrating emerging molecular biomarkers, such as DNA methylation signatures and circulating tumor DNA, into routine clinical practice [116,117]. Advances in genomic and immunological profiling offer the potential to transform surveillance from reactive detection to proactive risk stratification, enabling more personalized disease management. Concurrently, incorporating chemopreventive agents[131,132] with established safety and cost-effectiveness profiles, such as 5-ASA, might contribute to modifying disease progression.

Advances in artificial intelligence-assisted endoscopy and confocal laser endomicroscopy might significantly improve dysplasia detection in patients with UC[117]. Prospective studies are warranted to validate liquid biopsy technologies and establish the clinical utility of non-invasive imaging tools for real-time risk stratification. Personalized medicine approaches that integrate molecular, clinical, and environmental risk factors offer a promising avenue for transforming caCRC prevention and early detection paradigms.

FOOTNOTES

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