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REVIEW

Colorectal cancer in inflammatory bowel disease: review of the evidence

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Abstract
Inflammatory bowel disease (IBD)-related colorectal cancer (CRC) is responsible for approximately 2% of the annual mortality from CRC overall, but 10–15% of the annual deaths in IBD patients. IBD-related CRC patients are also affected at a younger age than sporadic CRC patients, and have a 5-year survival rate of 50%. Despite optimal medical treatment, the chronic inflammatory state inherent in IBD increases the risk for high-grade dysplasia and CRC, with additional input from genetic and environmental risk factors and the microbiome. Recognizing risk factors, implementing appropriate surveillance, and identifying high-risk patients are key to managing the CRC risk in IBD patients. Chemoprevention strategies exist, and studies evaluating their efficacy are underway. Once dysplasia or invasive cancer is diagnosed, appropriate surgical resection and postoperative treatment and surveillance are necessary. Here, we discuss the current state of IBD-related CRC, prevalence, risk factors, and evidence for surveillance, prophylaxis, and treatment recommendations.

Keywords Inflammatory bowel disease · Crohn's disease · Ulcerative colitis · Colorectal cancer · Screening · Colonoscopy · Chemoprophylaxis

Introduction and current state

Colorectal cancer (CRC) is the second most common cancer and cause of cancer-associated death in Europe [1]. There is a general trend of declining CRC-associated mortality most likely due to increased screening, earlier stage detection, and improved treatment options [2]. However, this trend is not seen in inflammatory bowel disease-related CRC (IBD-CRC), specifically ulcerative colitis (UC) and Crohn's disease (CD) patients.

The incidence and prevalence of IBD is increasing worldwide, with approximately 2.5–3 million Europeans affected [3]. In the European Union, there are an estimated 176,000 new IBD cases annually (53,000 CD and 123,000 UC) [4]. The prevalence of CD in Europe ranges from 1522 to 21312 cases/100,000 persons, and the prevalence of UC varies from 2422 to 2946 cases/100,000 persons [5]. This incidence and prevalence is associated with an estimated direct healthcare cost of 4.6–5.6 billion Euros/year to care for the IBD population [3].

IBD patients are 2–6 times more likely to develop CRC than the general population [6, 7]. Furthermore, when cancer does develop, IBD-CRC patients are affected at a younger age than sporadic CRC patients. IBD-CRC patients are 7.7 years younger than non-IBD CRC patients at diagnosis, with mean colitis-to-CRC intervals reported between 16 and 21 years [8]. In 2001, Bernstein, et al. reported an increased IBD-CRC incidence rate for both CD (2.64; 95% confidence interval [95% CI] 1.69–4.12) and UC (2.75; 95% CI 1.91–3.97) but an increased risk of rectal carcinoma only in UC (1.90; 95% CI 1.05–3.43) [9]. Other studies supported the overall increased CRC risk in UC, but with decreasing relative risk over time [7, 10, 11]. The risk of CRC associated with CD is more contentious. Studies reported the CRC-relative risk 2.5–4.5-fold higher in CD than in healthy subjects [12, 13]. These values have changed over time, and a CD diagnosis may no longer mean that the risk of CRC

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significantly increased [14–16]. However, there are biases in the assessment of IBD-CRC, including its relatively low prevalence, the aging of the study cohorts, and the clinically heterogeneous nature of IBD, which can effect reported rates [17, 18]. Nevertheless, CRC has a huge impact in this patient population and IBD-CRC is responsible for 10–15% of deaths in IBD patients each year [19].

Risk factors

Several known variables impact the risk of IBD-CRC. Age at diagnosis and disease duration are strong, independent risk factors [7, 20]. In general, CRC risk begins to increase 8–10 years after the diagnosis is made, and increases over time. The incidence rates corresponded to cumulative probabilities for IBD-CRC of 2% by 10 years, 8% by 20 years, and 18% by 30 years [10]. The extent of mucosal inflammation and portion of the bowel affected are other risk factors [12]. Pancolitis patients are at higher risk, with prevalence of 5.7% [10]. Patients with left-sided UC are also at higher risk for IBD-CRC; however, patients with ulcerative proctitis have a CRC risk similar to that of the general population [21]. In CD, the relative risk of IBD-CRC is highest in patients with colonic disease and lowest in isolated ileal disease [12, 13, 22]. CD patients with penetrating disease and who have had immunosuppressive therapy are also at significantly higher risk of IBD-CRC [23]. The presence of UC and concomitant primary sclerosing cholangitis (PSC) is another risk. A study from the Swedish Cancer Registry found that patients with an intact colon when diagnosed with PSC had a cumulative CRC risk of 16% after 10 years, while those with UC prior to diagnosis of PSC had a cumulative risk of 25% (24).

Geography plays a role in IBD-CRC development. The risk is higher in North America and the UK than in Scandinavian countries with no evidence of temporal impact [12]. In the US and UK, the annual risk of IBD-CRC is 4–5 cases/1000 person-years, whilst in Scandinavian and other countries it is 2 cases/1000 person-years [6]. The reason for geographic heterogeneity is multifactorial, including genetics, diet, chemoprevention, and differences in colonoscopic surveillance [6]. As with sporadic CRC, family history is associated with increased risk. IBD patients with CRC in a first-degree relative have twice the risk of developing CRC than those who do not [24]; patients with a first-degree relative diagnosed with CRC before 50 have a ninefold higher relative risk [25]. Finally, a personal history of CRC and previous or synchronous colorectal adenomas are risk factors for IBD-CRC. The Gastrointestinal Oncology Group of the Spanish Gastroenterological Association reported that patients with a personal history of CRC [odds ratio (OR), 5.58, 95% CI 1.01–31.01], and presence of previous or synchronous adenomas (OR, 1.77; 95% CI 1.21–3.17) have a significantly increased risk.

The molecular and bacterial basis for IBD-CRC

Molecular alterations that occur in sporadic CRC, such as chromosomal instability, microsatellite instability (MSI) and hypermethylation, play a role in IBD-CRC, but the order and frequency of these mutations, and the fact that they often occur before definite histologically defined dysplasia, differentiates IBD-CRC from sporadic CRC [26] (Fig. 1). The initiation and development of IBD-CRC is linked to inflammation, and follows a sequence of genetic alterations following an "inflammation-dysplasia-carcinoma" sequence, not the "adenoma-sequence" classically described in sporadic CRC [27, 28]. The relationship between chronic inflammation and some molecular mediators that contribute to IBD-CRC are well established. Models highlight the role of toll-like receptors (TLR) and tumor necrosis factor-α (TNF-α) in the activation of nuclear factor κB (NFκB)—a master regulator of inflammation, which then induces transcription of tumorigenesis genes, including COX-2 [29–31]. The inflammation induces apoptosis of intestinal epithelial cells via tumor suppressor p53 pathways; defective signaling via p53 may be an early event in the progression of dysplasia to cancer [32]. The p53 mutations occur earlier in IBD-CRC than sporadic CRC. These p53 mutations are also often in grossly normal nondysplastic mucosa, a contrast to sporadic CRC [6]. The development of a nonfunctional adenomatous polyposis coli (APC) gatekeeper gene occurs later in IBD-CRC, just prior to carcinoma; this APC loss of function can occur because of chromosomal instability or MSI abnormalities, presenting in either polypoid or flat lesions [6]. IBD patients tend to have excessive inflammatory cell infiltration and expression of several inflammatory genes; this mucosal inflammation promotes cellular proliferation and ultimately CRC development [33]. With their increased presence in IBD-CRC compared to IBD without dysplasia, specific genetic mutations in KRAS and p53 could serve as biomarkers [34].

The dysbiosis of gut microbiota appears to have a role in IBD-CRC development [35, 36]. *E. coli*—a major contributor to the induction of chronic inflammation during IBD and convertor of IBD into CRC—is dramatically increased in IBD. The lipopolysaccharides of the gram-negative bacteria increase expression of TLR4, a common event during IBD-CRC tumorigenesis [37]. *E. coli* also activates NF-kB expression, which plays a role in inducing inflammation and CRC development. Colibactinequipped *E. coli*, an aggressive adherent invasive *E. coli* pathovar, are more prevalent in the colonic mucosa in CD and, to a lesser extent, UC patients [38]. Other organisms overrepresented in the tumor

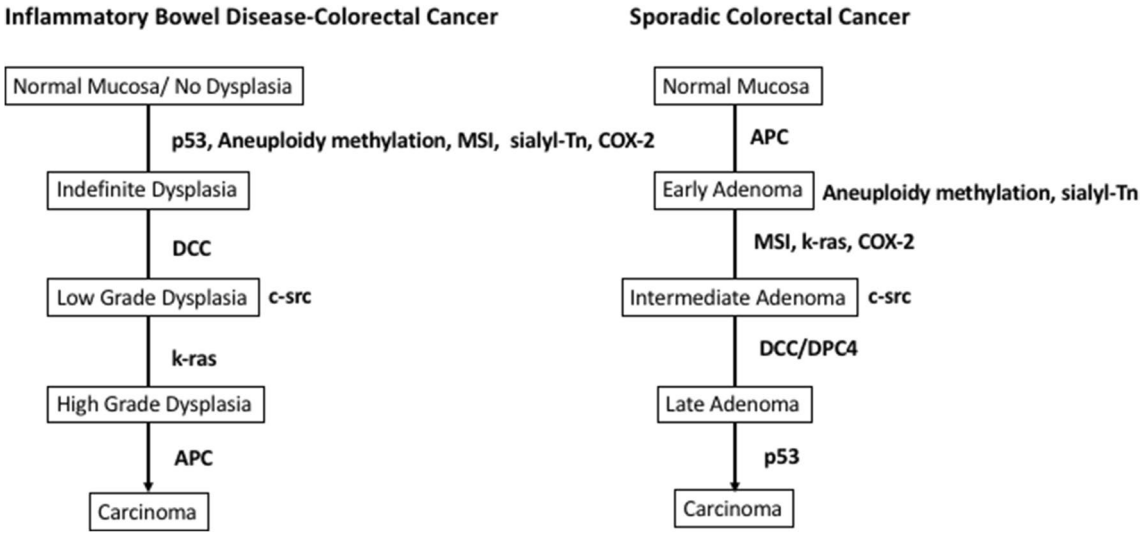

Fig. 1 Pathways to progression to colorectal cancer in sporadic and inflammatory bowel disease associated colorectal cancer

microenvironment may act as pro-inflammatory factors, contributing to IBD-CRC, including *Streptococcus bovis* and *Fusobacterium nucleatum* [39]. Understanding of the exact role of the microbiota dysbiotic component is continually evolving, and it will be exciting to search for therapeutic targets.

Chemoprophylaxis

Several agents have been evaluated for chemoprophylaxis, with varying results. A systematic review and meta-analysis in average and high-risk CRC patients evaluated potential benefits of several prophylactic agents; IBD patients were not specifically evaluated, but the outcome can be applied in general [40]. For patients with adenomas or CRC history, there was a significant 21% reduction in adenoma recurrence and a 26% reduction in CRC incidence. In individuals with a history of adenomas, calcium (1200–2000 mg/day) demonstrated a significant 18% reduction in the risk of adenoma recurrence. There was no significant effect with folic acid or antioxidants (vitamins A, C and E, beta carotene or selenium) on adenoma recurrence or incidence. Non-steroidal anti-inflammatory agents, such as Celecoxib (400 mg/day), had a significant 34% reduction in adenoma recurrence and a 55% reduction in advanced adenoma incidence. In CRC survivors, nonsteroidal anti-inflammatory drugs (NSAIDS) are associated with a threefold decreased risk of recurrence and sevenfold decreased risk of death [41].

IBD is a non-modifiable risk factor for CRC; however, there is a role for chemoprophylaxis with pharmacological therapy to reduce the inflammation and causative organisms that increase the risk of CRC [42]. Although it is accepted that chronic inflammation promotes colon cancer and chronic inflammation is the main cause of IBD-CRC, the mechanisms involved are not clear [43]. Suppressing inflammation should lower the risk for IBD-CRC, but studies have not established that the anti-inflammatory agents most commonly used to treat IBD have chemopreventive effects against cancer. Effective anti-inflammatory chemoprophylactic agents are Sulfasalazine and the 5-aminosalicylic acid (5-ASA) agents. Treatment with Sulfasalazine lasting at least 3 months was associated with a significant protective effect independent of disease activity [44]. A recent meta-analysis supported the chemopreventive effect of 5-aminosalicylic acid (5-ASA) agents in dosage $\geq$ 1.2 g/day in patients with IBD, with a significant additional effect in UC. The agents were effective only against CRC, not dysplasia [45]. Other work has shown mesalamine is associated with risk reduction in the same dosage [46]. Anti-TNF agents induce and maintain mucosal healing in moderate-to-severe IBD and, as a result, likely provide chemopreventative benefits by reducing long-standing chronic inflammation [47]. TNF-alpha has been reported to promote inflammation and IBD-CRC by promoting deoxynucleic acid (DNA) damage, stimulating angiogenesis, and inducing expression of COX-2, which also induces angiogenesis to promote tumor growth. In murine models, TNF-α expression was associated with the development of colonic tumors, while TNF-R blockade reduced inflammation and tumor development [48]; the effect was specifically seen with mice given the anti-TNF agents infliximab and etanercept [48, 49]. Although early investigations into the molecular mechanisms of TNF-α in IBD have suggested that TNF blockers may have a direct antineoplastic role, to date studies in humans have not established that these agents prevent colon neoplasia [47].

An emerging prophylactic agent for prevention of carcinogenesis is probiotic bacteria. Mouse models of CRC have shown that producing conjugated linoleic acid activates PPARγ, which inhibits COX-2 and induces apoptosis [50]. Further study is needed to validate this in human IBD-CRC.

Screening and surveillance guidelines

The aim of surveillance is to detect early dysplasia, and colonoscopy remains the gold standard in diagnosing intraepithelial neoplasia, dysplasia, or cancer in IBD [51]. Screening and surveillance is key to early detection, treatment, and prevention of CRC, but no randomized controlled studies have shown that surveillance colonoscopy in IBD patients reduces the risk of CRC. While the association between IBD and CRC is well established, there are still concerns regarding timely diagnosis and treatment of early neoplastic lesions. Dysplastic lesions in IBD may occur as flat or raised mucosal lesions, and are differentiated by the terms dysplasia-associated lesion or mass (DALM)-macroscopically flat or raised lesions without proper delineation to the surrounding mucosa- and adenoma-like mass (ALM)-sporadic adenomas that are similar to those observed in non-IBD patients (Fig. 2; Table 1). IBD-CRC does not follow the classic adenoma-sequence; the progression to dysplasia is believed to be more rapid than the progression of adenomas to CRC in the non-IBD population [21].

Guidelines from the European Crohn's and Colitis Organization (ECCO), the American Gastroenterological Association (AGA), the British Society of Gastroenterology (BSG) and the Association of Coloproctology for Great Britain and Ireland (ACPGBI) agree that IBD patients are "high risk" CRC, and surveillance colonoscopies should be started 8 years after the onset of pancolitis or 12–15 years after onset of left-sided and CD colitis, to assess disease extent and other endoscopic risk factors. However, there are discrepancies across guideline recommendations regarding the time interval between routine studies [52–54]. Colonoscopy surveillance is recommended to reassess disease extent every 1–2 years with biopsies for dysplasia [53, 54]. During surveillance, 2–4 random biopsies should be taken every 10 cm along the entire colon, with additional samples in suspicious areas, and 4-quadrant biopsy every 5 cm in the lower sigmoid and rectum. To aid detection, chromoendoscopy or pancolonic dye spraying with targeted biopsy of abnormal areas is recommended. If a dysplastic polyp is detected within an area of inflammation and can be removed in its entirety, colectomy is not necessary. Post colectomy, yearly flexible sigmoidoscopy of pouch/rectal mucosa in patients is recommended in higher risk patients-(previous dysplasia or CRC at the time of pouch surgery, primary sclerosing cholangitis, mucosa exhibiting atrophy, or severe pouch inflammation). Lower risk post-colectomy patients can consider 5-yearly flexible sigmoidoscopy of the pouch/rectal mucosa if none of the aforementioned risk factors are present, taking four proximal and four distal pouch biopsies [55].

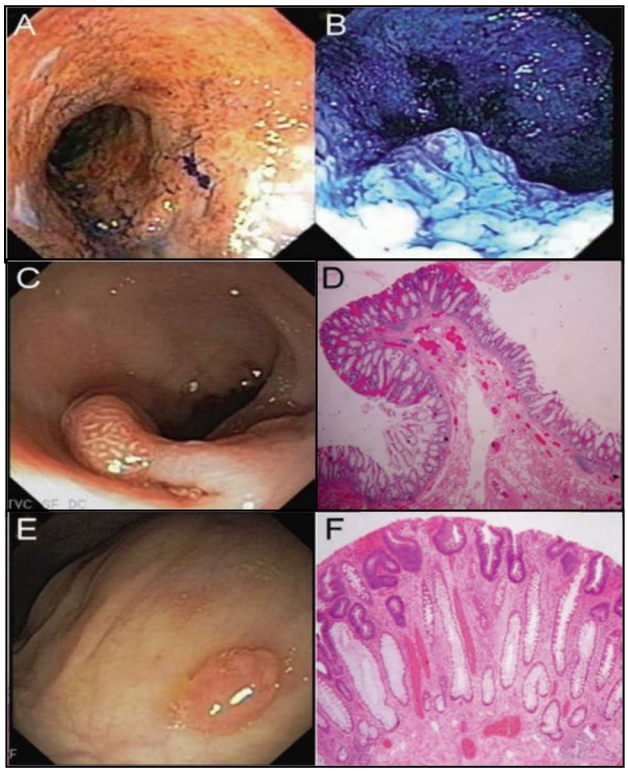

Fig. 2 Dysplasia-associated lesion or mass (DALM), adenomatous lesions, and ALM comparison. **a** Endoscopic view of a DALM under white light; **b** endoscopic view of a DALM with chromoendoscopy; **c** endoscopic view of an adenoma; **d** histology of an adenoma; **e** endoscopic view of an adenoma-like mass (ALM); **f** histology of an ALM

For the first time, the BSG has recommended the use of high-definition endoscopy chromoendoscopy or pancolonic dye spraying with targeted biopsy of abnormal areas [55]. This technique involves spraying a dye, such as indigo carmine or methylene blue, onto the mucosa to enhance visualization of subtle mucosal changes associated with dysplasia or neoplasia. With these tools, dysplasia, previously thought to be 'invisible' to the endoscopist, is now considered to be 'visible' [56]. This has implications for changing the paradigm of treating dysplastic lesions, where endoscopic resection can be considered, rather than radical surgery. Further studies are needed to determine its efficacy in this high-risk patient population, as well as if the additional training required offers a cost effective solution. Dye-based and magnification chromoendoscopy improve detection of dysplasia, and evaluation of inflammatory activity and extension of UC (Fig. 3). Chromoendoscopy has proved highly effective and several guidelines suggest its use with a target biopsy

Table 1 Dysplastic lesions in inflammatory bowel disease

Type	Inflammation	Macroscopic view	Neighboring tissue	Treatment
Dysplasia-associated lesion or mass (DALM)	In an area of inflammation	Single or multiple polyps, plaques or velvety patches	Surrounded by flat dysplasia, endoscopically challenging to detect amidst inflammation	Surgical resection
Adenoma-like mass (ALM)	Not in an area of inflammation	Well-circumscribed polyp, amenable to endoscopic resection	Not surrounded by flat dysplasia, endoscopically indistinguishable from a sporadic polyp	Endoscopic excision with circumferential biopsies to rule out neighboring inflammation

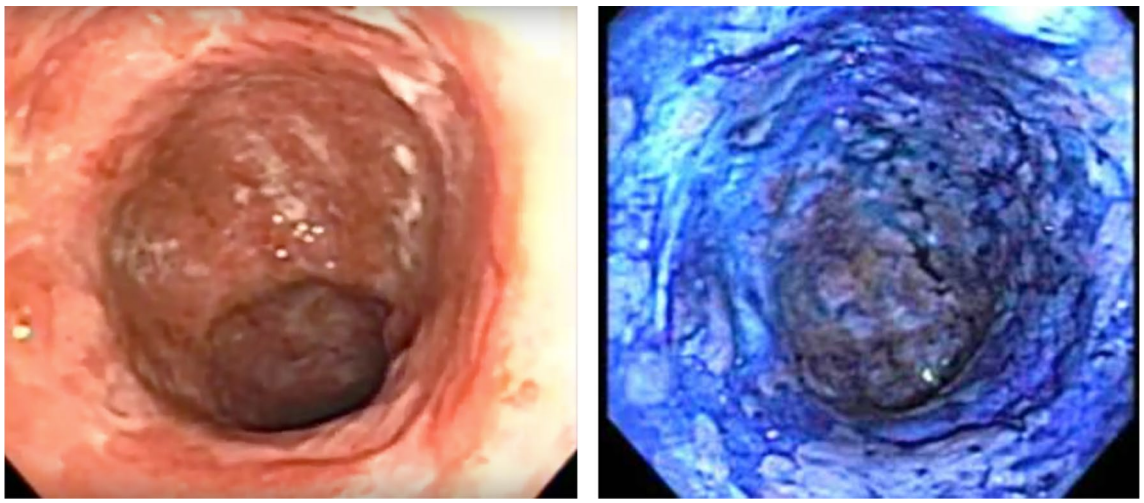

Fig. 3 Ulcerative colitis colonoscopic view with white light and blue chromoemdoscopy dye

[19]. Chromoendoscopy with confocal laser endomicroscopy (CLE) is reported to detect 4.75-times more neoplasms than conventional colonoscopy, while requiring 50% fewer biopsy specimens; it is not a technology for lesion detection alone, though [57]. This combination is most useful to identify areas of suspicion in IBD surveillance. However cost, availability, and experience are still an issue [58]. Dye-less chromoendoscopy modalities, including narrow band imaging, iScan, and autofluorescence imaging, can also enhance surveillance in comparison to white light endoscopy with optical or electronic filter technologies, but the evidence to recommend routine use is lacking [59].

Whilst the current surveillance protocol is recommended for IBD patients, no randomized studies demonstrate a risk reduction in CRC development or mortality due to surveillance colonoscopy, but indirect evidence suggests surveillance reduces the risk of death [60, 61]. There is evidence that cancer can generally be detected at an earlier stage with surveillance colonoscopy and that these patients have a better prognosis. Lutgens et al. found the 5-year survival rate after an IBD-CRC diagnosis was 100% in patients undergoing standard surveillance, compared to 74% in those not participating in surveillance, and more tumors were found at an early stage in the surveillance group [62]. A recent Cochrane review affirmed that endoscopic surveillance prolongs life by allowing earlier detection of CRC and dysplastic pre-cursor lesions in IBD [63]. The pooled analysis found the surveillance group had a significantly lower rate of CRC detection (1.83% vs. 3.17%, OR 0.58, 95% CI 0.42–0.80; $p=0.0009$), earlier stage CRC detection (16% vs. 8%, OR 5.40, 95% CI 1.51–19.30; $p=0.009$), and a lower mortality (8% vs. 22%, OR 0.36, 95% CI 0.19–0.69, $p=0.002$), respectively [63].

Close clinical follow-up needs to be performed with IBD patients in addition to surveillance colonoscopy for cancer prevention. Issues of compliance with biopsy protocols and undersampling have been reported. In the UK: more than 50% of the gastroenterologists survey obtained fewer than ten colonic mucosal biopsies per examination [64]. In addition, while current guidelines recommend increased surveillance for CRC in this population, adherence remains poor and timing may not be adequate for detection. Much endoscopic surveillance is performed without following internationally recommended guidelines, rendering screening in

this population ineffective [65, 66]. A University of Minnesota study reported that almost 50% of their IBD-CRC patients had their cancer diagnosed because increased colitis symptoms led to colonoscopic examination outside of surveillance, and 18% of patients developed cancer with less than an 8-year history of IBD [67]. Another study from the Cancer Registry of Norway reported 21% of CRC in their registry study developed before 10 years since IBD diagnosis, and therefore, before the usual recommended time for starting colonoscopic screening [68]. By relying solely on surveillance guidelines, these cancers could have been missed. Thus, further study should be focused on reassessing and increasing adherence to appropriate guidelines.

Surgical indications and treatment course

Recommendations for surgery are guided by screening and surveillance findings. High-grade dysplasia (HGD), multifocal dysplasia, and invasive carcinoma are an absolute indication for surgery. DALM harbors a high risk of progression to CRC, and is also a colectomy indication. There is over a 50% risk of developing cancer within 5 years of the diagnosis of dysplasia, and patients with DALM have a 20–30% risk of harboring an unrecognized synchronous or metachronous CRC [69–71]. Therefore, DALM patients are recommended to have prophylactic proctocolectomy with ileoanal pouch. Newer endoscopic excision techniques, such as en-bloc resection of the lesion with Endoscopic Submucosal Dissection or Endoscopic Mucosal Resection, have been described for resection of DALM and ALM when paired with chromoendoscopy and close surveillance. However, there is no long-term follow-up of outcomes, or controlled comparative studies of endoscopic resection vs. surgical resection, and so resection remains the best practice for DALM. In contrast, ALM patients can be treated with standard polypectomy and endoscopic surveillance with little risk of subsequent malignancy [72, 73]. The need for complete excision in both lesions is stressed, as a high proportion of unresectable lesions harbor cancer [74] (Fig. 4).

There is debate on the need for resection after low-grade dysplasia (LGD) is discovered. Both HGD and LGD are risk factors for IBD-CRC, and the likelihood of finding synchronous cancer at colectomy is 42% with HGD and 19% with

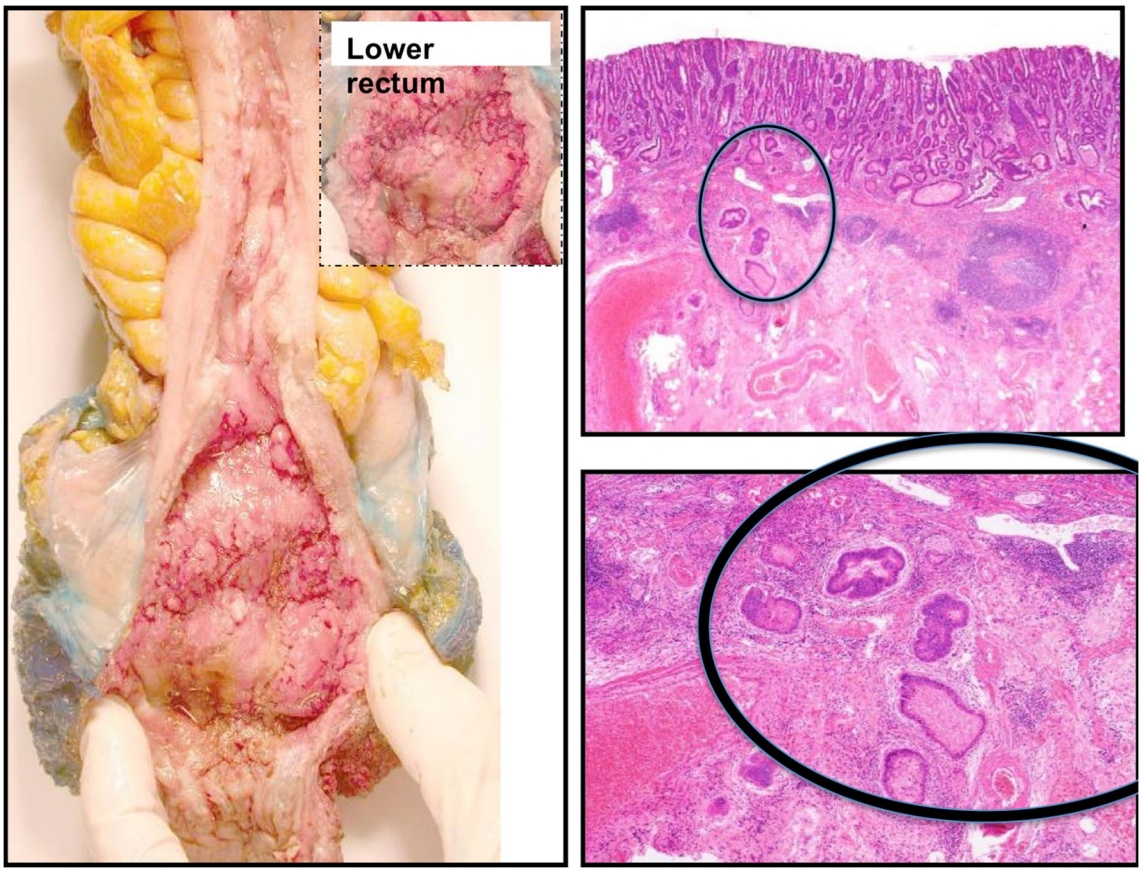

Fig. 4 Rectal moderately differentiated adenocarcinoma in a Crohn's disease patient. Gross specimen, moderate, and high power histopathology views

LGD [52]. The variability in the risk of progression from LGD to HGD or cancer—is 0–50%—leading to controversy about management [75, 76]. Ullman et al. reported a 53% 5-year progression rate to HGD or CRC in UC patients with LGD discovered on surveillance colonoscopy [69]. Connell et al. found similar 5-year progression rates of 54% in long-term surveillance [75]. While it has been proven that LGD can develop into DALM, HGD, and invasive cancer, the time to progression is unknown [76]. Thus, consideration of colectomy is valid with LGD. Wide variations in the perceptions and management of LGD in IBD were seen in a survey of British Society of Gastroenterology members [77]. Seventy percent of respondents considered LGD premalignant, but only 13% offered routine colectomy, compared with 84% for HGD. Eighty-five percent considered LGD with DALM high-risk for concurrent CRC, but only 53% offered total colectomy. Patients were more likely to be treated with colectomy for flat HGD (77%) and HGD in the presence of DALM (86%). Thus, there is a need for more research and consensus on LGD surgical recommendations.

In addition, any patient unable or unwilling to have routine surveillance endoscopy should have surgery discussed to circumvent the risk of IBD-CRC. When the decision is made to have surgery, a treatment course decided by the multidisciplinary team, including the surgeon, gastroenterologist, pathologist, oncologist, and the patient, is needed to optimize outcomes [78]. The goal of surgery in IBD-CRC is to remove all disease and tissue at risk with a complete oncological resection while preserving quality of life. The specific surgical plan varies depending on the diagnosis of UC or CD, the lesion location, the patient's comorbidities, and personal wishes. IBD-CRC has greater propensity to develop in the proximal colon than sporadic CRC, and is significantly less likely to be located in the rectum compared to sporadic CRC [79]. The stage of cancer distribution is similar for IBD-CRC and sporadic CRC patients, but IBD-CRC tumors are often mucinous, and there is a higher frequency of multiple, synchronous tumors (OR 4.403, 95% CI 2.32–8.36; $p < 0.001$) and poor differentiation (OR 1.59–1.86, 95% CI 1.26–2.47; $p < 0.001$) [6, 67, 79–81]. Considering the rates of synchronous dysplasia and lesions, under ideal conditions, the surgical procedure of choice in IBD-CRC—both UC and CD—is a total proctocolectomy (TPC) with ileal-pouch anal anastomosis (IPAA) [82]. These recommendations are consistent with population studies that demonstrate IBD-CRC patients—both UC and CD—were more likely to have total colectomy or panproctocolectomy than partial colectomy compared to non-IBD CRC patients [83]. In CD, segmental resection was formerly recommended to spare bowel and prevent Crohn's disease of the pouch [84]. However, the diagnosis of adenocarcinoma is often not known at the time of resection, and a segmental resection would not guarantee appropriate oncological resection [78]. Furthermore, neoplasia in CD behaves similarly to UC, supporting a more extensive UC-like surgical approach of TPC with end ileostomy, instead of a segmental resection, as the optimal course [85]. An IPAA is also an option in CD. IPAA procedures were historically discouraged in patients with known CD due to high rates of complications and subsequent pouch excision [86, 87]. However, there has been something of a change in the management paradigm. While reported, CD of the pouch remains poorly defined and the diagnosis is often made on a non-specific clinical picture; actual pouch loss rates are low and functional results are favorable [88–90]. Thus, IPAA can be recommended in select cases of CD as an alternative to total protocolectomy with definitive end-ileostomy, with the patient well informed of the risks, failure rates, and functional results [87, 91]. Under less optimal conditions, including patient comorbidities, function, and personal preferences, lesser procedures may be made on an individual basis. These procedures for UC include a TPC with permanent ileostomy, subtotal colectomy with ileorectal anastomosis (IRA), segmental resection, and palliative procedures such as diverting colostomy or ileostomy (Fig. 5). For a total abdominal colectomy with a stapled anastomosis, there are a few centimeters of colonic

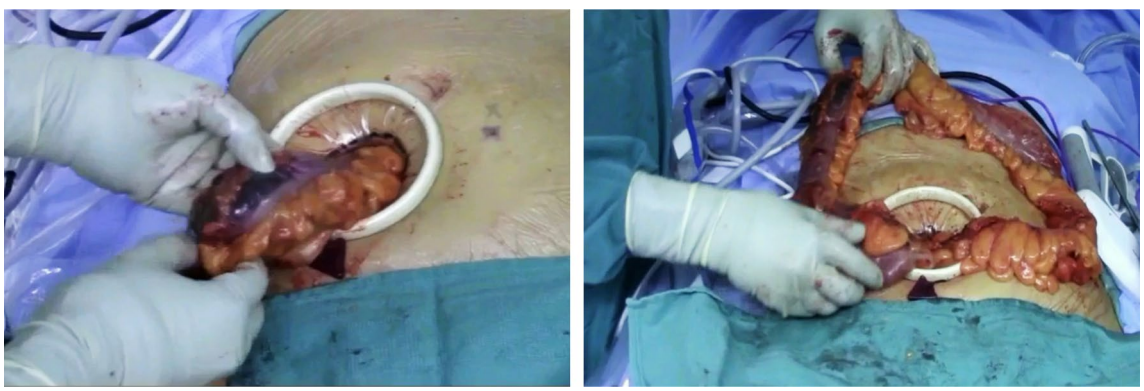

Fig. 5 Single incision laparoscopic total abdominal colectomy with end ileostomy creation, as part of a staged total proctocolectomy procedure

mucosa (1–2 cm) are left in situ below anastomosis, with a risk of malignant degeneration. The hand-sewn IPAA with mucosectomy reduces the risk of retained colonic mucosa below the anastomosis, but does not allow complete removal of columnar epithelium, which can progress to a malignant state [92]. This highlights the need for continued surveillance after surgery.

Postoperative course and prognosis

Postoperatively, IBD adversely impacts outcomes. A review of the National Inpatient Sample and Nationwide Readmissions Database showed IBD-CRC patients had longer length of stay, greater likelihood of postoperative complications, including wound infection and deep vein thrombosis, and were more likely to be readmitted within 30 days than sporadic CRC patients [83]. CD patients specifically were more likely to develop postoperative hemorrhage, hematoma or seroma, wound dehiscence, and poor wound healing [83].

Given the tumorigenetic and histomorphological differences between IBD-CRC and sporadic CRC, different treatment responses could be present. The current data supports the same indications for adjuvant chemotherapy. A morphologic similarity between IBD-CRC and microsatellite instability high (MSI-H) CRC, with less response and higher risk of intestinal toxicity from fluorouracil-based chemotherapy was previously reported [93, 94]. However, the largest study to date comparing oncologic outcomes in IBD-CRC to sporadic CRCs found no significant differences, and supports fluorouracil-based chemotherapy in IBD-CRC [95]. Patients with histologically active IBD also did not require chemotherapy alterations compared to inactive IBD patients [96]. Further prospective studies are needed to guide therapeutic decisions.

Long-term, IBD-CRC has higher recurrence and higher mortality rates than sporadic CRC [67, 80, 97]. A matched analysis reported local recurrence was three times higher ($p=0.004$) and 5-year survival significantly lower in IBD-CRC than sporadic CRC (49% vs. 67%, $p=0.03$) [97]. A meta-analysis of 3472 patients indicated IBD-CRC patients had shorter survival than sporadic CRC patients (HR 1.24, 95% CI 1.19–1.29) [80]. In a recent case-matched study IBD-CRC patients had a significantly shorter median survival than sporadic CRC (68.2 vs. 204.3 months, $p=0.01$); Stage 3 IBD-CRC patients specifically showed significantly decreased survival (23.0 vs. 133.9 months, $p=0.008$). On multivariate analysis, after adjusting for N and M stage, IBD was associated with an increased risk of death compared to sporadic CRC (HR 2.011, 95% CI 1.24–3.23, $p=0.004$) [98]. Patients with stage IV IBD-CRC also had shorter survival than patients without IBD [96]. Thus, intensive surveillance and early treatment are essential [99]. More robust studies on long-term outcomes for IBD-CRC are needed. Recently, an international cross-disciplinary working group addressed this issue, and proposed a standardized set of patient-centered outcome measures for IBD, including domains of survival, CRC, and disease control [100]. This international template could facilitate better outcomes data in this population going forward.

There is little data on postoperative CD treatment after surgery for IBD-CRC. There is also no compelling evidence that anti-TNF therapy plays a role in solid tumor development. All IBD-CRC patients should receive multidisciplinary management, with collaboration between gastroenterologists and oncologists, and must be based on the individual case, considering IBD activity, concomitant therapy, patient age, and the cancer type and stage [101]. 5-ASA agents and non-systemic steroids should be first line; thiopurines, calcineurin inhibitors, and anti-TNF agents should be stopped at least until cancer therapy is completed [101]. Preliminary data demonstrate no obvious risk of developing a new or recurrent cancer while being treated with anti-TNF therapy. Further research is needed on the topic for definitive recommendations.

Conclusions

The risk of developing CRC is increased in IBD, and affected patients have a worse outcome than patients with sporadic CRC. The increased CRC risk in IBD is thought to be due to chronic inflammatory state, with new theories emerging about additional risk factors. Recognizing these factors, implementing appropriate surveillance, and identifying high-risk patients are key to managing IBD-CRC. Several surveillance strategies are recommended to identify these lesions, and new endoscopic technology is emerging to identify the colitis-associated neoplasms more precisely than random biopsies. When dysplasia is discovered, surgery remains the most conservative option, with further evidence needed on the outcomes with endoscopic resection. After resection, evidence-based guidelines advise surveillance to manage the risk of recurrent dysplasia and CRC. Further study is needed on adjuvant treatment for CRC and CD treatment after surgery.

Author contributions DSK: substantial contribution to the conception, design of the work and consensus of topics; acquisition, synthesis, and interpretation of data for the work; drafting the work and revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. AW: substantial contribution to the conception, design of the work and consensus of topics; synthesis and interpretation of data for the work; revising the work critically for important intellectual content;

final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. RC: substantial contribution to the conception, design of the work and consensus of topics; synthesis and interpretation of data for the work; revising the work critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. MC: substantial contribution to the conception, design of the work and consensus of topics; synthesis and interpretation of data for the work; revising the work critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Compliance with ethical standards

Conflict of interest DK, AW, RC, and MC declared no conflicts of interest.

Ethical approval As there was no data analysis or patient involvement in this review, this work was exempt from the institutional review board process.

Informed consent For this type of study, formal consent is not required.

References

1. Ferlay J, Soerjomataram I, Dikshit R et al (2015) Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 136:E359–E386
2. Bradley CJ, Lansdorp-Vogelaar I, Yabroff KR et al (2011) Productivity savings from colorectal cancer prevention and control strategies. Am J Prev Med 41:e5–e14
3. Burisch J, Jess T, Martinato M, Lakatos PL, ECCO E (2013) The burden of inflammatory bowel disease in Europe. J Crohns Colitis 7:322–337
4. Loftus EVJ (2004) Clinical epidemiology of inflammatory bowel disease: incidence, prevalence, and environmental influences. Gastroenterology 126:1504–1517
5. Gheorghe C, Pascu O, Gheorghe L et al (2004) Epidemiology of inflammatory bowel disease in adults who refer to gastroenterology care in Romania: a multicentre study. Eur J Gastroenterol Hepatol 16:1153–1159
6. Mattar MC, Lough D, Pishvaian MJ, Charabaty A (2011) Current management of inflammatory bowel disease and colorectal cancer. Gastrointest Cancer Res 4:53–61
7. Ekbom A, Helmick C, Zack M, Adami HO (1990) Ulcerative colitis and colorectal cancer. A population-based study. N Engl J Med 323:1228–1233
8. Brackmann S, Andersen SN, Aamodt G et al (2009) Two distinct groups of colorectal cancer in inflammatory bowel disease. Inflamm Bowel Dis 15:9–16
9. Bernstein CN, Blanchard JF, Kliewer E, Wajda A (2001) Cancer risk in patients with inflammatory bowel disease: a population-based study. Cancer 91:854–862
10. Eaden JA, Abrams KR, Mayberry JF (2001) The risk of colorectal cancer in ulcerative colitis: a meta-analysis. Gut 48:526–535
11. Mellemkjaer L, Olsen JH, Frisch M, Johansen C, Gridley G, McLaughlin JK (1995) Cancer in patients with ulcerative colitis. Int J Cancer 60:330–333
12. von Roon AC, Reese G, Teare J, Constantinides V, Darzi AW, Tekkis PP (2007) The risk of cancer in patients with Crohn's disease. Dis Colon Rectum 50:839–855
13. Canavan C, Abrams KR, Mayberry J (2006) Meta-analysis: colorectal and small bowel cancer risk in patients with Crohn's disease. Aliment Pharmacol Ther 23:1097–1104
14. Jess T, Simonsen J, Jørgensen KT, Pedersen BV, Nielsen NM, Frisch M. Decreasing risk of colorectal cancer in patients with inflammatory bowel disease over 30 years. Gastroenterology. 2012;143:375.e1–381.e1 **(quiz e13)**
15. Jess T, Loftus EV, Velayos FS et al (2006) Risk of intestinal cancer in inflammatory bowel disease: a population-based study from olmsted county, Minnesota. Gastroenterology 130:1039–1046
16. Kappelman MD, Farkas DK, Long MD et al. Risk of cancer in patients with inflammatory bowel diseases: a nationwide population-based cohort study with 30 years of follow-up evaluation. Clin Gastroenterol Hepatol. 2014;12:265.e1–273.e1
17. Tsianos (2000) Risk of cancer in inflammatory bowel disease (IBD). Eur J Intern Med 11:75–78
18. Lutgens MW, van Oijen MG, van der Heijden GJ, Vleggaar FP, Siersema PD, Oldenburg B (2013) Declining risk of colorectal cancer in inflammatory bowel disease: an updated meta-analysis of population-based cohort studies. Inflamm Bowel Dis 19:789–799
19. Fornaro R, Caratto M, Caratto E et al (2016) Colorectal cancer in patients with inflammatory bowel disease: the need for a real surveillance program. Clin Colorectal Cancer 15:204–212
20. Rutter MD, Saunders BP, Wilkinson KH et al (2006) Thirty-year analysis of a colonoscopic surveillance program for neoplasia in ulcerative colitis. Gastroenterology 130:1030–1038
21. Ullman T, Odze R, Farraye FA (2009) Diagnosis and management of dysplasia in patients with ulcerative colitis and Crohn's disease of the colon. Inflamm Bowel Dis 15:630–638
22. van den Heuvel TR, Wintjens DS, Jeuring SF et al (2016) Inflammatory bowel disease, cancer and medication: cancer risk in the Dutch population-based IBDSL cohort. Int J Cancer 139:1270–1280
23. Scaringi S, Di Martino C, Zambonin D et al (2013) Colorectal cancer and Crohn's colitis: clinical implications from 313 surgical patients. World J Surg 37:902–910
24. Nuako KW, Ahlquist DA, Mahoney DW, Schaid DJ, Siems DM, Lindor NM (1998) Familial predisposition for colorectal cancer in chronic ulcerative colitis: a case–control study. Gastroenterology 115:1079–1083
25. Askling J, Dickman PW, Karlén P et al (2001) Family history as a risk factor for colorectal cancer in inflammatory bowel disease. Gastroenterology 120:1356–1362
26. Sebastian S, Hernández V, Myrelid P et al (2014) Colorectal cancer in inflammatory bowel disease: results of the 3rd ECCO pathogenesis scientific workshop (I). J Crohns Colitis 8:5–18
27. Feagins LA, Souza RF, Spechler SJ (2009) Carcinogenesis in IBD: potential targets for the prevention of colorectal cancer. Nat Rev Gastroenterol Hepatol 6:297–305
28. Itzkowitz SH, Yio X (2004) Inflammation and cancer IV. Colorectal cancer in inflammatory bowel disease: the role of inflammation. Am J Physiol Gastrointest Liver Physiol 287:G7–G17
29. Westbrook AM, Szakmary A, Schiestl RH (2010) Mechanisms of intestinal inflammation and development of associated cancers: lessons learned from mouse models. Mutat Res 705:40–59
30. Goel GA, Kandiel A, Achkar JP, Lashner B (2011) Molecular pathways underlying IBD-associated colorectal neoplasia: therapeutic implications. Am J Gastroenterol 106:719–730

31. McConnell BB, Yang VW (2009) The role of inflammation in the pathogenesis of colorectal cancer. Curr Colorectal Cancer Rep 5:69–74
32. Dirisina R, Katzman RB, Goretsky T et al (2011) p53 and PUMA independently regulate apoptosis of intestinal epithelial cells in patients and mice with colitis. Gastroenterology 141:1036–1045
33. Velayos FS, Loftus EV, Jess T et al (2006) Predictive and protective factors associated with colorectal cancer in ulcerative colitis: a case–control study. Gastroenterology 130:1941–1949
34. Bezzio C, Festa S, Saibeni S, Papi C (2017) Chemoprevention of colorectal cancer in ulcerative colitis: digging deep in current evidence. Expert Rev Gastroenterol Hepatol 11:339–347
35. Kang M, Martin A (2017) Microbiome and colorectal cancer: unraveling host-microbiota interactions in colitis-associated colorectal cancer development. Semin Immunol 32:3
36. Grivennikov SI (2013) Inflammation and colorectal cancer: colitis-associated neoplasia. Semin Immunopathol 35:229–244
37. McCoy AN, Araújo-Pérez F, Azcárate-Peril A, Yeh JJ, Sandler RS, Keku TO (2013) Fusobacterium is associated with colorectal adenomas. PLoS One 8:e53653
38. Arthur JC, Perez-Chanona E, Mühlbauer M et al (2012) Intestinal inflammation targets cancer-inducing activity of the microbiota. Science 338:120–123
39. Khan AA, Khan Z, Malik A et al (2017) Colorectal cancer-inflammatory bowel disease nexus and felony of *Escherichia coli*. Life Sci 180:60
40. Cooper K, Squires H, Carroll C et al (2010) Chemoprevention of colorectal cancer: systematic review and economic evaluation. Health Technol Assess 14:1–206
41. Johnson CC, Jankowski M, Rolnick S, Yood MU, Alford SH (2014) Influence of NSAID use among colorectal cancer survivors on cancer outcomes. Am J Clin Oncol
42. Haggar FA, Boushey RP (2009) Colorectal cancer epidemiology: incidence, mortality, survival, and risk factors. Clin Colon Rectal Surg 22:191–197
43. Ullman TA, Itzkowitz SH (2011) Intestinal inflammation and cancer. Gastroenterology 140:1807–1816
44. Pinczowski D, Ekbom A, Baron J, Yuen J, Adami HO (1994) Risk factors for colorectal cancer in patients with ulcerative colitis: a case–control study. Gastroenterology 107:117–120
45. Qiu X, Ma J, Wang K, Zhang H (2017) Chemopreventive effects of 5-aminosalicylic acid on inflammatory bowel disease-associated colorectal cancer and dysplasia: a systematic review with meta-analysis. Oncotarget 8:1031–1045
46. O'Connor A, Packey CD, Akbari M, Moss AC (2015) Mesalamine, but Not sulfasalazine, reduces the risk of colorectal neoplasia in patients with inflammatory bowel disease: an agent-specific systematic review and meta-analysis. Inflamm Bowel Dis 21:2562–2569
47. Chapman CG, Rubin DT (2014) The potential for medical therapy to reduce the risk of colorectal cancer and optimize surveillance in inflammatory bowel disease. Gastrointest Endosc Clin N Am 24:353–365
48. Poutahidis T, Haigis KM, Rao VP et al (2007) Rapid reversal of interleukin-6-dependent epithelial invasion in a mouse model of microbially induced colon carcinoma. Carcinogenesis 28:2614–2623
49. Kim YJ, Hong KS, Chung JW, Kim JH, Hahm KB (2010) Prevention of colitis-associated carcinogenesis with infliximab. Cancer Prev Res (Phila) 3:1314–1333
50. Bassaganya-Riera J, Viladomiu M, Pedragosa M, De Simone C, Hontecillas R (2012) Immunoregulatory mechanisms underlying prevention of colitis-associated colorectal cancer by probiotic bacteria. PLoS One 7:e34676
51. Neumann H, Vieth M, Langner C, Neurath MF, Mudter J (2011) Cancer risk in IBD: how to diagnose and how to manage DALM and ALM. World J Gastroenterol 17:3184–3191
52. Guagnozzi D, Lucendo AJ (2012) Colorectal cancer surveillance in patients with inflammatory bowel disease: what is new. World J Gastrointest Endosc 4:108–116
53. Annese V, Daperno M, Rutter MD et al (2013) European evidence based consensus for endoscopy in inflammatory bowel disease. J Crohns Colitis 7:982–1018
54. Rex DK, Boland CR, Dominitz JA et al (2017) Colorectal cancer screening: recommendations for physicians and patients from the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology 153:307–323
55. Cairns SR, Scholefield JH, Steele RJ et al (2010) Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (update from 2002). Gut 59:666–689
56. Abraham BP (2016) Cancer surveillance in ulcerative colitis and Crohn's disease: new strategies. Curr Opin Gastroenterol 32:32–37
57. Kiesslich R, Goetz M, Lammersdorf K et al (2007) Chromoscopy-guided endomicroscopy increases the diagnostic yield of intraepithelial neoplasia in ulcerative colitis. Gastroenterology 132:874–882
58. Gabbani T, Manetti N, Bonanomi AG, Annese AL, Annese V (2015) New endoscopic imaging techniques in surveillance of inflammatory bowel disease. World J Gastrointest Endosc 7:230–236
59. Cheon JH (2015) Advances in the endoscopic assessment of inflammatory bowel diseases: cooperation between endoscopic and pathologic evaluations. J Pathol Transl Med 49:209–217
60. Lashner BA, Kane SV, Hanauer SB (1990) Colon cancer surveillance in chronic ulcerative colitis: historical cohort study. Am J Gastroenterol 85:1083–1087
61. Karlén P, Kornfeld D, Broström O, Löfberg R, Persson PG, Ekbom A (1998) Is colonoscopic surveillance reducing colorectal cancer mortality in ulcerative colitis? A population based case control study. Gut 42:711–714
62. Lutgens MW, Oldenburg B, Siersema PD et al (2009) Colonoscopic surveillance improves survival after colorectal cancer diagnosis in inflammatory bowel disease. Br J Cancer 101:1671–1675
63. Bye WA, Nguyen TM, Parker CE, Jairath V, East JE (2017) Strategies for detecting colon cancer in patients with inflammatory bowel disease. Cochrane Database Syst Rev 9:CD000279
64. Eaden JA, Ward BA, Mayberry JF (2000) How gastroenterologists screen for colonic cancer in ulcerative colitis: an analysis of performance. Gastrointest Endosc 51:123–128
65. van Rijn AF, Fockens P, Siersema PD, Oldenburg B (2009) Adherence to surveillance guidelines for dysplasia and colorectal carcinoma in ulcerative and Crohn's colitis patients in the Netherlands. World J Gastroenterol 15:226–230
66. Feuerstein JD, Lewandowski JJ, Martinez-Vazquez M, Leffler DA, Cheifetz AS (2015) Documented compliance with inflammatory bowel disease quality measures is poor. Dig Dis Sci 60:339–344
67. Mayer R, Wong WD, Rothenberger DA, Goldberg SM, Madoff RD (1999) Colorectal cancer in inflammatory bowel disease: a continuing problem. Dis Colon Rectum 42:343–347
68. Brackmann S, Andersen SN, Aamodt G et al (2009) Relationship between clinical parameters and the colitis-colorectal cancer interval in a cohort of patients with colorectal cancer in inflammatory bowel disease. Scand J Gastroenterol 44:46–55
69. Ullman TA (2003) Patients with low-grade dysplasia should be advised to undergo colectomy. Inflamm Bowel Dis 9:267–269 **(discussion 273)**

70. Bach JF (2002) The effect of infections on susceptibility to autoimmune and allergic diseases. N Engl J Med 347:911–920
71. DeRoche TC, Xiao SY, Liu X (2014) Histological evaluation in ulcerative colitis. Gastroenterol Rep (Oxf) 2:178–192
72. Engelsgjerd M, Farraye FA, Odze RD (1999) Polypectomy may be adequate treatment for adenoma-like dysplastic lesions in chronic ulcerative colitis. Gastroenterology 117:1288–1294; **(discussion 1488)**
73. Odze RD, Farraye FA, Hecht JL, Hornick JL (2004) Long-term follow-up after polypectomy treatment for adenoma-like dysplastic lesions in ulcerative colitis. Clin Gastroenterol Hepatol 2:534–541
74. Rutter MD, Saunders BP, Wilkinson KH, Kamm MA, Williams CB, Forbes A (2004) Most dysplasia in ulcerative colitis is visible at colonoscopy. Gastrointest Endosc 60:334–339
75. Connell WR, Lennard-Jones JE, Williams CB, Talbot IC, Price AB, Wilkinson KH (1994) Factors affecting the outcome of endoscopic surveillance for cancer in ulcerative colitis. Gastroenterology 107:934–944
76. Jess T, Loftus EV, Velayos FS et al (2006) Incidence and prognosis of colorectal dysplasia in inflammatory bowel disease: a population-based study from Olmsted County, Minnesota. Inflamm Bowel Dis 12:669–676
77. Thomas T, Nair P, Dronfield MW, Mayberry JF (2005) Management of low and high-grade dysplasia in inflammatory bowel disease: the gastroenterologists' perspective and current practice in the United Kingdom. Eur J Gastroenterol Hepatol 17:1317–1324
78. Althumairi AA, Lazarev MG, Gearhart SL (2016) Inflammatory bowel disease associated neoplasia: a surgeon's perspective. World J Gastroenterol 22:961–973
79. Reynolds IS, O'Toole A, Deasy J, McNamara DA, Burke JP (2017) A meta-analysis of the clinicopathological characteristics and survival outcomes of inflammatory bowel disease associated colorectal cancer. Int J Colorectal Dis 32:443–451
80. Ou B, Zhao J, Guan S, Lu A (2016) Survival of colorectal cancer in patients with or without inflammatory bowel disease: a meta-analysis. Dig Dis Sci 61:881–889
81. Larsen M, Mose H, Gislum M et al (2007) Survival after colorectal cancer in patients with Crohn's disease: a nationwide population-based Danish follow-up study. Am J Gastroenterol 102:163–167
82. Panis Y (1998) Is there a place for ileal pouch-anal anastomosis in patients with Crohn's colitis. Neth J Med 53:S47–S51
83. Ramsey M, Krishna SG, Stanich PP et al (2017) Inflammatory bowel disease adversely impacts colorectal cancer surgery short-term outcomes and health-care resource utilization. Clin Transl Gastroenterol 8:e127
84. Coviello LC, Stein SL (2014) Surgical management of nonpolypoid colorectal lesions and strictures in colonic inflammatory bowel disease. Gastrointest Endosc Clin N Am 24:447–454
85. Svrcek M, Cosnes J, Beaugerie L et al (2007) Colorectal neoplasia in Crohn's colitis: a retrospective comparative study with ulcerative colitis. Histopathology 50:574–583
86. Deutsch AA, McLeod RS, Cullen J, Cohen Z (1991) Results of the pelvic-pouch procedure in patients with Crohn's disease. Dis Colon Rectum 34:475–477
87. Keighley MR (2000) The final diagnosis in pouch patients for presumed ulcerative colitis may change to Crohn's disease: patients should be warned of the consequences. Acta Chir Iugosl 47:27–31
88. Melton GB, Fazio VW, Kiran RP et al (2008) Long-term outcomes with ileal pouch-anal anastomosis and Crohn's disease: pouch retention and implications of delayed diagnosis. Ann Surg 248:608–616
89. Tekkis PP, Heriot AG, Smith O, Smith JJ, Windsor AC, Nicholls RJ (2005) Long-term outcomes of restorative proctocolectomy for Crohn's disease and indeterminate colitis. Colorectal Dis 7:218–223
90. Lightner AL, Fletcher JG, Pemberton JH, Mathis KL, Raffals LE, Smyrk T (2017) Crohn's disease of the pouch: a true diagnosis or an oversubscribed diagnosis of exclusion. Dis Colon Rectum 60:1201–1208
91. Panis Y, Poupard B, Nemeth J, Lavergne A, Hautefeuille P, Valleur P (1996) Ileal pouch/anal anastomosis for Crohn's disease. Lancet 347:854–857
92. Gentilini L, Coscia M, Laureti S, Poggioli G (2011) Surgery in presence of dysplasia in IBD. Ann Ital Chir 82:37–40
93. Liu X, Goldblum JR, Zhao Z et al (2012) Distinct clinicohistologic features of inflammatory bowel disease-associated colorectal adenocarcinoma: in comparison with sporadic microsatellite-stable and Lynch syndrome-related colorectal adenocarcinoma. Am J Surg Pathol 36:1228–1233
94. Tiersten A, Saltz LB (1996) Influence of inflammatory bowel disease on the ability of patients to tolerate systemic fluorouracil-based chemotherapy. J Clin Oncol 14:2043–2046
95. Dugum M, Lin J, Lopez R et al (2017) Recurrence and survival rates of inflammatory bowel disease-associated colorectal cancer following postoperative chemotherapy: a comparative study. Gastroenterol Rep (Oxf) 5:57–61
96. Axelrad J, Kriplani A, Ozbek U et al (2017) Chemotherapy tolerance and oncologic outcomes in patients with colorectal cancer with and without inflammatory bowel disease. Clin Colorectal Cancer 16:e205–e210
97. Renz BW, Thasler WE, Preissler G et al (2013) Clinical outcome of IBD-associated versus sporadic colorectal cancer: a matched-pair analysis. J Gastrointest Surg 17:981–990
98. Hrabe JE, Byrn JC, Button AM, Zamba GK, Kapadia MR, Mezhir JJ (2014) A matched case–control study of IBD-associated colorectal cancer: IBD portends worse outcome. J Surg Oncol 109:117–121
99. Kim BJ, Yang SK, Kim JS et al (2009) Trends of ulcerative colitis-associated colorectal cancer in Korea: a KASID study. J Gastroenterol Hepatol 24:667–671
100. Kim AH, Roberts C, Feagan BG et al (2017) Developing a standard set of patient-centred outcomes for inflammatory bowel disease—an international, cross-disciplinary consensus. J Crohns Colitis 12:408
101. Annese V, Beaugerie L, Egan L et al (2015) European evidence-based consensus: inflammatory bowel disease and malignancies. J Crohns Colitis 9:945–965