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# Preface

In recent decades, there have been tremendous gains in our understanding of the pathogenesis of inflammatory bowel diseases (IBDs), including both ulcerative colitis (UC) and Crohn's disease (CD). Patients with these diseases have a high risk of developing colorectal cancer (CRC), specifically, colitis-associated cancer (CAC), as the repeated episodes of inflammation act as chronic oncogenic insults to the colonic epithelium. In addition, patients with CD, in which the chronic inflammation also involves the small intestine, are at high risk of developing small-bowel adenocarcinoma.

CAC differs from sporadic CRC, both in its histopathological and genetic characteristics. In IBD, the chronic inflammation leads to the increased turnover of epithelial cells, resulting in both low-grade and high-grade dysplasia, and therefore, over time, CAC. This sequence of tumorigenic events is different to that leading to sporadic CRC, although genetic and epigenetic alterations characterize both. CAC has thus been the focus of detailed investigations regarding protein expression; the roles played by the immune response, cytokines, and oxidant stress; the gut bacterial flora; and several other features that contribute to tumorigenesis in patients with IBD.

Despite the extensive experience that has accumulated over many years of managing IBD patients, the diagnosis and treatment of CAC remain controversial. There is widespread agreement regarding the need for surveillance to improve the probability of the early diagnosis of CAC, which is essential given its rapid progression, the poor prognosis of patients diagnosed at a younger age, and the higher mortality associated with CAC than with sporadic CRC. However, whether surveillance reduces CAC-related mortality is unclear. An additional problem is that, in patients with CD, surveillance colonoscopy is difficult because of the presence of colonic strictures, such that most CD-associated CACs and small-bowel tumors are diagnosed in the advanced stage, which implies a poor prognosis. Moreover, surveillance guidelines differ between countries, and a gold standard with respect to endoscopic devices and sampling (e.g., frequency and location) has yet to be defined. Most clinicians recognize the limitations of random biopsy based

on its low yield in detecting neoplasia. Instead, chromoendoscopy with targeted biopsies has gained acceptance, and newer endoscopic techniques are being evaluated.

Important advances have been made in the treatment of IBD, although curative treatments remain elusive. In patients with newly detected CAC, surgery, ranging from endoscopic resection to abdominoperineal resection and total proctocolectomy, is the definitive therapeutic approach. However, both the indications for endoscopic treatment and whether the therapeutic benefits of chemotherapy and radiation therapy are the same in CAC as in sporadic CRC are matters of debate. A recent area of investigation is a chemopreventative approach aimed at reducing the inflammation in IBD and thereby also the risk of CAC. Thus, probiotics, immune modulators, and other anti-inflammatory agents are currently being tested.

Basic research into the pathophysiology of IBD has included genome-wide association analysis and the identification of susceptibility genes. These findings have the potential to change clinical practice, predict the natural history of the disease in a particular patient, and guide the choice of therapy. Epigenetics; novel, potentially diagnostic biomarkers; and prognostic markers for CAC have been identified. Molecular alterations in the non-neoplastic mucosa of UC patients, so-called field effects, are promising biomarkers that allow the identification of patients at high risk of CAC. Based on the differential patterns of these markers, it may be possible to predict the progression to carcinogenesis and the responsiveness to therapy. This will give rise to new, patient-tailored therapeutic approaches and more objective surgical indications.

This book provides both an overview of the results of the latest studies on IBD and a summary of the knowledge we have gained through our own experience. It is our hope that, through its brief but informative chapters, readers will acquire a deeper understanding of CAC.

Tsu, Japan M. Kusunoki

# Contents

# Chapter 1
# Colitis-Associated Cancer: Overview

**Masato Kusunoki**

**Abstract** In this book, we discuss the pathogenesis and management of colitis-associated colorectal cancer (CAC), including its incidence, risk factors, and prognosis, the genetic alterations leading to tumorigenesis, disease prevention and surveillance options, and medical and surgical treatments.

Among patients with inflammatory bowel diseases (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), CAC is one of the most important causes of mortality. The first reports of CAC (Crohn and Rosenberg. Am J Med Sci 170:220–228, 1925; Warren and Sommers. Gut 48(4):526–535, 2001) showed that its biology and underlying mechanisms distinguish it from sporadic colorectal cancer (CRC). Thus, many different aspects of CAC, such as the histopathological, genetic features, protein expression, the role of the immune response, cytokine disorders, and oxidant stress, and the gut bacterial flora of these patients have been the focus of numerous investigations. Together, they have provided a comprehensive description of the development of CAC.

**Keywords** Ulcerative colitis • Colorectal cancer • Dysplasia • Diagnosis • Treatment

## 1.1 Characteristics of CAC in UC

The increased risk of the development of UC-associated CAC (UC-CAC) [1, 2] has been attributed to both genetic and acquired factors. Among the risk factors for developing UC-CAC are the duration [3–5], extent [3, 4, 6–9], and severity [10–13] of colitis, the presence of postinflammatory polyps (pseudopolyps) [10, 12, 14–16], young age at UC onset [3, 6–8], male gender [7, 9], a family history of sporadic CRC [15, 17], and the coexistence of primary sclerosing cholangitis [4, 18, 19]. However, the most important and well-recognized risk factors for UC-CAC are the duration and extent of colitis.

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UC-CAC shows a more proximal distribution in the colon than CRC, has a higher frequency of multiple synchronous colorectal tumors, and exhibits more aggressive growth and early metastases [20]. CAC tends to be distributed in several locations and to be of higher histologic grade than sporadic cancer [21]. However, according to a report examining each cancer stage, there is no significant difference in the prognosis of CAC vs. sporadic CRC [21–23]. Nonetheless, in the former there is a higher prevalence of mucinous carcinomas [21, 24, 25], which have a relatively worse prognosis than other histologic types of colorectal cancers.

## 1.2 Role of Endoscopy in UC-CAC

Although recent technical progress in gastroenterological endoscopy, it is still difficult to discriminate between the neoplasms of CC-CAC. This remains the case for dysplasia, which can be difficult to distinguish from normal inflamed mucosa especially in a flat lesion. Thus, surveillance colonoscopy is recommended for the earlier detection and improved prognosis of UC-CAC. Surveillance colonoscopy has been standardized and is now broadly recognized in several guidelines as necessary in patients with long-standing colitis (>8–10 years) in whom there is extended pancolitis or left-sided colitis [26–30]. The prognosis of CAC is considered to better in UC patients who have undergone surveillance colonoscopy than in those who have not [31, 32]. However, in recent guidelines, there are some minor variations regarding the timing of initial screening colonoscopy and the surveillance interval, depending on whether risk stratification has been applied [33–36]. The generally recommended method of surveillance colonoscopy is quadrantic biopsies randomly sampled every 10 cm throughout the colon [33–36]. However, because random biopsy has a low detection rate [37], its use is increasingly discouraged; instead there is increasing focus on target biopsies supported by chromoendoscopy or other newer endoscopic techniques [38–40].

For surveillance, chromoendoscopy allows the detection of dysplasia [38, 41, 42]. The borders of the lesion can be sharply defined using indigo carmine dye spraying as the contrast method. Newer endoscopic techniques, including narrow-band imaging [43], fluorescence endoscopy [44, 45], optical coherence tomography [46], and confocal endomicroscopy [41, 46, 47], are being explored as tools to aid in the diagnosis of dysplasia in IBD. Narrowband imaging, a form of virtual chromoendoscopy, can provide a clear image of the microvascular structure, but it is not an alternative to chromoendoscopy for the surveillance for dysplasia [48]. In autofluorescence imaging, the purple-colored neoplasia stands out against the greenish background of normal colonic tissue [49, 50]; however, its effectiveness in UC-CAC remains to be determined. Fluorescence endoscopy commonly employs the blue-fluorescent dye 5-aminolevulinic acid as the sensitizer, based on its selective accumulation in malignant and premalignant tissue [51, 94]. Confocal laser endomicroscopy allows for instant in vivo histology during the course of a standard endoscopy and provides an approximately 1000-fold magnification; but

limited data are available thus far [41, 47, 49, 52, 53]. Although there are as yet no randomized controlled trials confirming the effectiveness of surveillance colonoscopy, the Research Group of Intractable Inflammatory Bowel Disease of the Ministry of Health, Labour and Welfare of Japan has conducted a randomized controlled study to compare the efficacy of step biopsy and target biopsy [54]. The results of this study will be reported in the near future.

Total colectomy is currently the gold standard for UC-CAC, because the detection of metachronous neoplasia in the remnant colon and rectum after local resection remains challenging. In low-grade dysplasia (LGD), in which the margins can be diagnostically defined, endoscopic resection can provide an accurate histological diagnosis, but it is technically difficult because in UC the inflammation and fibrosis result in a submucosal layer that is substantially thinner than that of healthy individuals. However, adenoma-like masses (ALMs) can be successfully removed in UC patients using standard polypectomy techniques, with little risk of subsequent malignancy on follow-up [55–58]. In these cases, accurate pathological diagnosis is very important in distinguishing between an ALM and a dysplasia-associated lesion or mass (DALM).

In general, it is often difficult to histologically distinguish dysplasia from non-dysplasia, even by an expert pathologist. Thus, surveillance colonoscopy should be performed during remission phases, which increases the accuracy of histological diagnosis. This is particularly important with respect to the endoscopic resectability of a lesion and in determining its extent; the latter takes precedence over deciding whether the lesion is an ALM or a DALM [5].

## 1.3 Characteristics of CD-Associated Cancer

The risk of CRC in long-standing CD involving the colon is the same as that in UC [59–62] although the prevalence of CD-associated cancer (CD-CAC) has been increasing. Although the prognosis of CD-CAC is unclear and a wide range of relative risk estimates have been published [63], most reports on the incidence of CD-CAC have been based on patients with a more advanced stage of disease and lymph node involvement than was the case in studies of UC-CAC or non-IBD-related CRC [33, 64–67]. Moreover, CD is associated with a significantly increased risk of small bowel cancer (SBC) [68–71], although it occurs in $<1$ % of CD patients [72, 73]. Nonetheless, the prognosis of cancer, and especially of SBC, against a background of CD is poor because early detection is difficult because of the absence of characteristic symptoms and the difficulty in differentiating malignant disease from CD-related symptoms [74, 75]. In addition, the presence of severe, chronic, complicated, perianal disease in patients with CD seems to be associated with an increased risk of cancer in the anal canal. Carcinoma arising from a perianal fistula, especially a long-standing one, occurs more frequently in patients with CD than in the healthy population [68, 76–81].

## 1.4 Detection of CAC and SBC in CD

Cancer surveillance programs are thought to reduce the death rate from CD-CAC in patients with colonic disease [82, 83], but there are few data supporting their effectiveness. Moreover, cancer surveillance is often difficult in patients with CD, regardless of the anatomical location of the cancer, because examinations may be limited by the presence of colonic stricture. Thus, up to one-third of patients with IBD develop CAC prior to the initial surveillance [65–67]. Surveillance colonoscopy in patients with CD involving the colon is recommended to assess disease extent and other endoscopic risk factors at least 8–10 years after the onset of disease symptoms [33, 64, 84]. Screening colonoscopy is also recommended in patients with CD colitis involving at least one-third of the length of the colon [35, 84]. The screening interval is based on the estimated risk and on disease duration beginning with the onset of symptoms [33, 84].

The early detection of SBC in patients with CD also remains challenging. A screening and surveillance program for SBC has yet to be established. Routine magnetic resonance enteroclysis/enterography or capsule endoscopy may allow detection of these malignancies at an early stage. However, whether the routine use of these techniques in the screening of asymptomatic individuals can prolong the survival of patients with CD is unclear. Moreover, given the high costs of these procedures, their use remains controversial.

Symptoms in patients with cancer arising from perineal fistulas in CD are usually nonspecific. Consequently, there are no formal guidelines for the screening and surveillance of cancers associated with CD in the lower rectum and perianal region. Carcinoma arising in a CD fistula can be very difficult to diagnose, because the examination for anorectal lesions may be limited by pain, stricture, or induration of the perianal and perineal tissues [80, 85]. Imaging studies, including computed tomography, magnetic resonance imaging (MRI), and 18-fluorodeoxyglucose positron emission tomography (FDG-PET), have a low sensitivity for detecting cancer [80, 85]. Therefore, a high degree of suspicion for carcinoma must be considered in a patient with CD undergoing a rectal examination under anesthesia. The recommended techniques include biopsy, curettage, and brushing of the fistulous tract [86].

## 1.5 Prevention of CAC

Because chronic inflammation of the large bowel is an important factor for the development of CAC, recent studies have recognized the long-term failure to achieve remission from active colitis as a risk factor [12, 21]. Accordingly, the use of anti-inflammatory agents as chemopreventive agents has been considered. In fact, the most common maintenance therapy in patients with IBD is 5-aminosalicylate. However, while a meta-analysis initially revealed its protective

effect with respect to CAC [87], this was not confirmed in subsequent investigations [13, 88–90]. The discrepancy has yet to be resolved. Data on the potential chemopreventive effect of thiopurines in IBD are likewise conflicting [17, 65, 91–93].

Recent data from experimental colitis models have indicated that TNF-α has a tumor-promoting effect [94], and the effect of antibodies targeting tumor necrosis factor (TNF)-α has therefore been evaluated. In a case-control study, anti-TNF-α was shown to protect against the development of CAC [16]. However, most of the studies on chemoprevention in CAC have been retrospective, and various biases have affected their results. This is especially the case when more than one medication was administered for IBD. Thus, whether chemopreventive agents have a role to play in reducing the occurrence of CAC in IBD patients is still unclear.

## 1.6 Molecular Pathways for CAC

The early detection of IBD-related cancer requires an understanding of the molecular pathways of IBD itself. As noted above, CAC exhibits obvious differences from sporadic CRC with regard to tumor biology. Epithelial cells are sensitive to the balance between pro-and anti-tumorigenic immune factors during inflammation. While colonic inflammation is associated with various tumorigenic events in CAC, their sequence is quite different from those that contribute to the development of sporadic CRC. Development of the latter is characterized as the adenoma → carcinoma sequence, which involves the stepwise accumulation of genetic abnormalities [95]. CAC, however, evolves from LGD to high-grade dysplasia (HGD) to carcinoma and involves multiple genetic alterations. In this process, the inflammatory condition, which consists of an increase in cytokines, chemokines, and reactive oxygen and nitrogen species (RONS), induces DNA mutations, epigenetic alterations, and genomic instability, all of which are well known to be associated with tumor initiation, promotion, and spread [96, 97]. Nonetheless, the molecular mechanisms by which chronic inflammation promotes cancer progression have yet to be fully elucidated.

As noted above, TNF-α is important in cancer development because it acts as a tumor initiator, by stimulating the production of molecules such as those that mediate oxidative stress [98–101]. TNF-α is upregulated in the blood and colonic mucosa of patients with IBD. In an in vivo study of a mouse model of colitis, the use of an anti-TNF-α monoclonal antibody reduced tumor development [97, 102]. Interleukin (IL)-6 is also important in CAC because it promotes the survival of neoplastic colonic epithelial cells [103–108]. The anti-inflammatory cytokine IL-10 downregulates TNF- α, vascular endothelial growth factor, and IL-6 production, which may also account for its inhibitory effect on the tumor stroma [109]. These observations demonstrate a role for the incorrect balance of both pro- and anti-inflammatory cytokines in inflammation and in inflammation-associated carcinogenesis. In fact, animal models have shown that the multifunctional transcription factor nuclear factor B (NF-kB) is required for colorectal neoplasia

[110]. Intraluminal bacterial endotoxins and pro-inflammatory cytokines act through extracellular receptors, such as Toll-like receptors (TLR), to initiate phosphorylation cascades that transmit signals to NF-kB [111, 112]. For example, TLR-4 is upregulated both in UC-CAC and in a mouse model of colon tumors [113].

Oxidative stress caused by the chronic inflammation characteristic of IBD increases the risk of colonic carcinogenesis [114] by inducing nitric oxide synthase, RONS, and free radicals [115–117]. It is also thought that oxidative stress disables the mismatch repair system and thereby causes genomic instability [118, 119]. Genomic instability can be divided into two clinically distinct forms that have been extensively studied in CRC: chromosomal instability (CIN) and microsatellite instability (MSI) [120].

CIN is typically associated with the progressive accumulation of mutations in onco-suppressor genes, such as the adenomatous polyposis coli (APC) and p53 genes, and oncogenes such as KRAS. Loss of APC function is a very common initiating event in sporadic CRC, but it is less frequent and usually occurs later in CAC [121–124]. Mutations in p53 are part of the early process of tumorigenesis, i.e., in preneoplastic lesions or those indefinite for dysplasia [125–127]. The loss of p53 function, observed in over half of the cases of CAC, is an important step in disease progression [125, 127, 128]. Conversely, the KRAS mutation plays a significant role in the later stage of CAC, as is the case in sporadic CRC [129], but its detection rate is lower in the former [130, 131].

MSI reflects alterations in or the inactivation of DNA repair mechanisms, including nucleotide excision repair, base excision repair, and mismatch repair [132]. An association of UC-CAC with MSI has been demonstrated, and the high rate of MSI in long-standing UC is probably related to the genomic instability produced by repeated inflammatory stimulations [133].

For both CIN and MSI, epigenetic elements can affect tumor initiation, proliferation, and metastasis in CAC. For example, the hypermethylation of onco-suppressor DNA promoter regions and microRNAs are two major epigenetic mechanisms of gene silencing that are involved in the development and progression of colorectal carcinogenesis [134]. Epigenetic alterations are also observed during inflammation and inflammation-associated carcinogenesis [135, 136]. The methylation of CpG islands in several genes precedes dysplasia and can be detected throughout the mucosa of patients with UC [137]. A significant relationship between DNA methylation and MSI in UC patients has been reported [138, 139]. Therefore, the inactivation of promoter hypermethylation may be critical in preventing the accumulation of inflamed, genetically damaged epithelial cells in UC and thus for preventing the initiation of the carcinogenetic process and the development of CAC. Inflammation-induced DNA methylation is related to oxidative stress and increased levels of pro-inflammatory cytokines [108, 140–142]. The mechanisms of how these pro-inflammatory mediators alter the DNA methylation pattern during inflammation are not completely understood, but in a mouse model of colitis, aberrant DNA methylation was detected even in the absence of macroscopic tumors and gradually increased until they developed

[143]. Therefore, the duration of inflammation is an important factor in aberrant DNA methylation, which is consistent with the duration of IBD being a risk factor for the development of CAC.

A role for microRNA (miRNA) has also been described. miRNA acts posttranscriptionally and is one of the major regulators of gene expression [144] during cellular differentiation, development, proliferation, and apoptosis. It also contributes to the initiation and progression of cancer in carcinogenesis [145]. In general, the expression profiles of tumor-specific miRNAs are more informative and discriminatory than mRNA profiles. Furthermore, circulating miRNAs are highly resistant to RNase activity, unlike mRNA [146]. There are reports showing higher miRNA levels in IBD-associated dysplastic lesions than in active IBD [147] and that the levels increase successively at each stage of IBD progression [148, 149]. However, miRNA-based markers for identifying UC patients who are at increased risk of neoplasia are still at the early stage of development, as described in the following section.

## 1.7 Molecular Markers for Identifying CAC

An improved prognosis of patients with CAC requires diagnosis of the disease at an early or precancerous stage and therefore more accurate diagnostic modalities, such as the analysis of p53 alterations for distinguishing neoplastic lesions from regenerative epithelium. The molecular alterations in gene expression and in the form of CIN, MSI, DNA aneuploidy, DNA methylation, and telomere shortening in nonneoplastic UC mucosa, so-called field effects, are being explored as promising biomarkers for use in identifying UC patients at high risk of CAC. In addition, because age-related methylation may be an important contributor to the acquired predisposition to colorectal neoplasia, it may serve as a molecular marker in this population [137, 150, 151].

## 1.8 Surgical Indications for UC-CAC

In UC patients, the detection of CAC on biopsy is an absolute indication for surgery. However, the decision-making process in patients with UC who, after a diagnosis of dysplasia, are considering intensive surveillance rather than surgical intervention is a difficult one. The detection of HGD is an absolute indication for surgical resection regardless of previous surgical treatment [25, 152]. Moreover, as noted above, any DALM, in particular one associated with a polypoid mass, indicates a high likelihood of the presence of synchronous or metachronous neoplasia, considered to be endoscopically unresectable [153]. Thus, patients with UC who are diagnosed with non-adenoma-like DALMs, regardless of the dysplasia grade detected on biopsy, should undergo colectomy [35, 153, 154]. Indeed,

advanced neoplasia can be found in association with dysplastic changes of any grade [155, 156]. However, the strategy for patients with LGD varies slightly according to the guidelines [35, 36, 64]. Although controversial, there is evidence to suggest that patients with flat, unifocal LGD should consider colectomy [28, 84].

Surgical procedures for neoplasia in patients with UC range from colonoscopic resection to total proctocolectomy (TPC). The choice of surgical treatment is influenced by the site and stage of the cancer, the functional state of the rectum, the presence of multifocal lesions, the patient's age, and the duration of UC [157]. Abdominoperineal TPC is the definitive treatment for the eradication of undiagnosed synchronous dysplasias and/or carcinomas and the prevention of subsequent metachronous lesions in UC; therefore, it is the only operation that will reliably eliminate the cancer risk in UC. However, this procedure requires permanent ileostomy, such that it is indicated mostly in patients with advanced-stage cancer of the rectum and anal canal and in patients with poor anal sphincter function, such as the older postpartum female.

The efficacy of segmental colectomy in patients with UC in long-term remission is a matter of debate. Generally, segmental resection of the colon should be avoided for CAC because of the high frequency of occult carcinomas and multifocal carcinogenesis, such that a residual lesion and therefore postoperative relapse is not rare [158]. If the colitis is totally quiescent or exhibits rectal sparing, total abdominal colectomy with ileorectal anastomosis (IRA) may be recommended as an option for UC patients with a single cancer in the colon. Low anterior resection (LAR) should be considered very carefully in patients with quiescent UC and rectal cancer or dysplasia because further proctocolectomy and IPAA would be difficult after LAR. In addition, a relapse of inflammation in the residual rectum must be taken into account. Subtotal colectomy with end ileostomy and a rectal stump pouch are less ideal options because of the retained rectum, which represents a continued cancer risk. While this procedure has previously been demonstrated as a safe treatment option, some of these patients will be satisfied with an ileostomy. Others may not be eligible because of their comorbidities and will refuse later pelvic pouch surgery.

## 1.9 TPC with IPAA for UC-CAC

The gold standard procedure for patients with UC is TPC with IPAA. Whether with or without mucosal proctectomy (stapled or hand-sewn IPAAs), these procedures are indicated for any colonic or rectal neoplasms in the surgically fit patient. However, controversy remains regarding these two procedures in UC-CAC because of the risk that the patient will later develop synchronous or metachronous neoplasias in the retained anal transitional zone (ATZ) mucosa. If stapled IPAA is performed, both long-term surveillance to monitor dysplasia and repeat biopsies from the remnant ATZ are required. Clearly, the presence of dysplasia in the ATZ is a contraindication for stapled IPAA. Moreover, hand-sewn IPAA is strongly

recommended especially for cancers or HGD outside the ATZ because the incidence of dysplasia after stapled IPAA is not trivial [124, 159–166]. By contrast, there have been several reports of cancer occurrence from the residual ATZ even after hand-sewn IPAA with mucosectomy [159, 167]. Thus, routine long-term endoscopic surveillance is recommended in patients with long-standing ileal pouches even after mucosectomy of the ATZ and especially in the presence of dysplasia or cancer in the proctocolectomy specimen.

## 1.10 Prognosis After Surgery for UC-CAC

The survival of patients with UC-CAC is slightly poorer than that of patients with sporadic CRC; however, the detection of UC-CAC at an early stage results in the similar survival of the two groups [21, 22]. For locally advanced rectal cancer in patients with UC, multimodality therapies such as chemotherapy and radiotherapy are required. Whether preoperative chemoradiotherapy reduces the incidence of postoperative complications is controversial [166, 168, 169]. The prognosis after surgery for UC-CAC depends on the presence of neoplasia in the ileal pouch and the overall outcome. Although the cumulative incidence of neoplasia involving the ileal pouch is very low, a history of colorectal neoplasia and chronic inflammation of the ileal mucosa, such as preoperative backwash ileitis, and postoperative pouchitis are risk factors associated with pouch neoplasia [170–175]. It is therefore recommended that patients with these risk factors be followed by endoscopy and random biopsies for the rest of their lives.

## 1.11 Treatment of CAC and SBC in CD

In the surgical treatment of cancer associated with CD, the malignancy should be diagnosed with respect to its location, i.e., small intestinal, colonic, or anorectal. Because SBC is less frequent and is difficult to detect prior to surgery, its final diagnosis is often made based on perioperative or postoperative pathological examination results [176]. For CD-associated cancers in general, although their early-stage detection is challenging, FDG-PET has shown promise in the assessment of these tumors [177]. The objective of surgery for cancer in CD is resection for cure or, when indicated, palliation and the removal of associated or discontinuous segments of inflammatory disease.

Segmental resection is the surgical approach for treating SBC in segmental CD. In patients with multiple strictures of the small bowel, concomitant strictureplasties should be performed in addition to resection of the malignant stricture. Prior to strictureplasty, each stricture should be biopsied, with the evaluation of frozen sections, to rule out the presence of synchronous cancers. Segmental resection is also the surgical procedure of choice for colonic cancer in segmental

CD. However, subtotal colectomy is chosen in patients with CD of the colon with malignant degeneration but rectal sparing.

TPC is generally performed for patients with CAC and pancolitis or with segmental colonic and rectal disease or with colonic and severe perianal disease. Whether TPC is required for colorectal cancer or dysplasia in CD, as is the case in UC, or whether segmental resection might be adequate remains controversial [178]. In CD, once dysplasia is identified, segmental resection is a more feasible option, especially if there has been a consistent lack of inflammation elsewhere in the intestinal tract [178]. By contrast, TPC should be performed in patients with multifocal colonic dysplasia or rectal dysplasia.

Cancer involving an internal or external fistula and occurring in combination with an intestinal lesion of CD is uncommon. In these cases, the early-stage detection of the disease is very difficult, such that most of these tumors are unresectable. Occasionally, however, a radical en bloc resection that includes the fistula is possible.

In CD, anal cancers are more often adenocarcinoma than squamous cell carcinoma. Mucinous adenocarcinoma, a more aggressive type of CRC [179], occurs in approximately 50 % of CD-CAC cases. The prognosis of cancer associated with anorectal lesions is poor, although some reports have suggested that it can be improved by preoperative chemoradiotherapy. There is no evidence regarding the efficacy of adjuvant chemoradiation in CD patients with anorectal adenocarcinoma. In fact, mucinous anorectal adenocarcinoma seems to respond poorly to chemoradiation [180–182].

In the great majority of patients, the surgical treatment of rectal and anal cancers associated with CD involves proctectomy. In addition, the colon should be resected or totally removed depending on the extent of the inflammation [77]. Treatment can be curative if the diagnosis is made early. Since rectal amputation is unavoidable for most patients with cancer associated with anorectal lesions, abdominoperineal resection is the most frequently employed procedure [183–185].

Postoperative complications often occur after surgery for anorectal cancer associated with CD. Among these, perineal wound infection may result in a persistent perineal sinus. The management strategy for perineal wound problems will depend on the patient's condition and the surgeon's preference. Great care is necessary intraoperatively, as postoperative sexual and urinary dysfunction often result from intraoperative autonomic nerve injury.

There are no data on the value and benefit of adjuvant therapy after curative resection of gastrointestinal cancers in CD. For the occasional patient with cancer complicating CD, the same recommendations for adjuvant therapy in sporadic CRC patients undergoing resection can be adopted.

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