Masato Kusunoki
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Masato Kusunoki
Mie University Graduate School of Medicine
Department of Gastrointestinal and Pediatric Surgery
Tsu, Japan

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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

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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.

M. Kusunoki (✉)
Department of Gastrointestinal and Pediatric Surgery, Division of Reparative Medicine, Institute of Life Sciences, Mie University Graduate School of Medicine, 2-174 Edobashi, Tsu, Mie 514-8507, Japan
e-mail: surgery2@clin.medic.mie-u.ac.jp

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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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Part I
Clinical Features

Chapter 2
Incidence and Risk Factors

Koji Tanaka, Toshimitsu Araki, Yuji Toiyama, Yoshiki Okita, Yasuhiko Mohri, and Masato Kusunoki

Abstract Epidemiological data indicate that inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), is the third highest risk condition for the development of colorectal cancer (CRC), namely, colitis-associated cancer (CAC). CD is also associated with an increased risk of small-bowel adenocarcinoma, in response to chronic inflammation of the small intestine. In studies published in the 1990s, the risk for CAC in IBD was approximately 7 % at 20 years after diagnosis. In recent studies, the overall incidence of CAC in IBD is lower, less than 5 % at 20 years. However, several factors, such as the longer duration of colitis, extensive or severer colitis, and coexistent primary sclerosing cholangitis, have continued to be important in the development of CRC in patients with IBD. Despite clinical and experimental investigations, the molecular mechanisms by which chronic inflammation promotes cancer progression are still unknown.

Keywords Chronic inflammation • Duration of colitis • Extensive colitis • Primary sclerosing cholangitis

2.1 Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is an idiopathic inflammatory disorder of the gastrointestinal tract that consists of two major forms: ulcerative colitis (UC) and Crohn's disease (CD) [1]. UC extends proximally from the anal verge and involves the entire colon or a part of it. The inflammation in UC is limited to the mucosal layer. By contrast, CD can affect any part of the gastrointestinal tract but typically involves the distal part of the small intestine (ileum) and the colon. The affected segments frequently show a discontinuous pattern. The inflammation is transmural and extends to all layers of the intestine.

IBD is characterized by episodes of remission and exacerbation. Despite various effective treatments, some patients experience frequent flares of inflammation or

K. Tanaka (✉) • T. Araki • Y. Toiyama • Y. Okita • Y. Mohri • M. Kusunoki
Department of Gastrointestinal and Pediatric Surgery, Mie University Graduate School of Medicine, 2-174 Edobashi, Tsu, Mie 514-8507, Japan
e-mail: qouji@clin.medic.mie-u.ac.jp

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develop treatment-resistant disease with chronic inflammation. IBD is associated with various intestinal and extraintestinal complications, with one of the most serious being the development of colorectal cancer (CRC) [2]. IBD patients are at a higher risk of CRC than the general population [3], although the pathogenesis of CRC in IBD is unknown.

2.2 Inflammation and Cancer

Chronic inflammation increases the risk of carcinogenesis in various organs [4], and the link between inflammation and cancer development is well recognized. The molecular biology, immune pathobiology, and genetics of IBD-associated CRC are the focuses of intense research [5].

A link between inflammation and cancer was determined approximately 150 years ago, when, in 1863, Rudolf Virchow discovered the presence of leukocytes in neoplastic tissues. He hypothesized that the "lymphoreticular infiltrate" reflected the origin of cancer at sites of chronic inflammation [6].

Epidemiological data also indicate that inflammation plays an important role in the initiation, promotion, and progression of many types of cancer [7]. Distinct host immune cells, cytokines, and chemical mediators participate in all steps of inflammation-related carcinogenesis: tumor initiation, promotion, progression, and metastasis [8]. Among the chronic inflammatory diseases linked to colorectal carcinogenesis, IBD is perhaps the most widely recognized.

2.3 Sporadic and Hereditary Colorectal Cancer

As the third most common malignancy, CRC is a major cause of cancer-related death worldwide [9, 10]. Sporadic CRC, the most common type of CRC, is thought to develop from benign adenomas. Fearon and Vogelstein characterized the development of sporadic CRC in their model of the adenoma→carcinoma sequence, in which genetic abnormalities accumulate in a stepwise manner and ultimately lead to the development of malignancy [11].

Hereditary CRC accounts for 5–10 % of all CRC cases [9, 10] and consists of two major types: familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC), also known as Lynch syndrome. FAP is an autosomal-dominant inherited disorder resulting from germ-line mutations in the adenomatous polyposis coli (APC) gene [12]. In patients with FAP, numerous adenomatous polyps develop, mainly in the colon and rectum. Although they are benign, they are at extremely high risk of becoming malignant. HNPCC, or Lynch syndrome, is also an autosomal-dominant inherited syndrome. It results from defective mismatch repair proteins that show high microsatellite instability [13]. Patients with HNPCC have a tendency to develop CRC and are at increased

risk of other cancers, such as endometrial, ovarian, gastric, small intestinal, hepatobiliary, pancreatic, upper urinary, prostate, brain, and skin cancers.

2.4 Colitis-Associated Cancer

IBD-associated CRC, or colitis-associated cancer (CAC), is a form of CRC arising in patients with IBD [14]. Chronic inflammation of the large bowel such as that which occurs in IBD is associated with the subsequent development of CRC [15], as the repeated flare-ups of inflammation characteristic of IBD often lead to oncogenic insults to colonic epithelial cells.

In 1925, Crohn and Rosenberg reported a case of rectal carcinoma complicating UC and postulated that the lesion developed as a late manifestation of UC [16]. In 1948, Warren and Sommers reported a case of adenocarcinoma of the ascending colon in a patient with CD complicating regional enteritis [17]. Much later, in 2005, CD was also shown to be associated with an increased risk of small-bowel adenocarcinoma, due to chronic inflammation of the small intestine [18].

IBD is the third highest risk condition for the development of CRC, after FAP and HNPCC. Unlike sporadic and hereditary CRC, CAC usually derives from a focal or multifocal dysplastic mucosa in areas of chronic inflammation via an inflammation→dysplasia→carcinoma sequence [2]. CAC accounts for 1–2 % of all cases of CRC and for 10–15 % of all deaths among IBD patients. It is thus one of the most important causes of mortality in IBD patients [1, 2].

2.5 Clinical Features of CAC

The clinical features of CAC are distinct from those of sporadic CRC and are reviewed below.

2.5.1 Age at Diagnosis

The mean age of CAC development in IBD patients is lower than that of sporadic CRC in the general population.

Several studies have examined the age of CAC development in patients with UC. In the meta-analysis by Eaden et al. [19], the mean age at UC-CAC diagnosis was 43.2 years. Lakatos et al. [20] reported a median age of 51 years at the time of UC-CAC diagnosis, which, in Hungary, is almost 15 years younger than that of sporadic CRC development in the general population. In the study of Watanabe et al. [21], the mean age at UC-CAC diagnosis was 56.8 years, younger than the

62.5 years of patients in the Japanese general population who are newly diagnosed with sporadic CRC.

2.6 Pathological Features of CAC

CAC frequently progresses from flat or nonpolypoid dysplasia to invasive adenocarcinoma. The tumors show aggressive growth and early metastasis [22].

In patients with UC, the rectum and the sigmoid colon are the most common sites of CAC. Compared with the general population, CAC arising in UC patients shows a more proximal distribution in the colon. Watanabe et al. [21] showed that UC-CAC tended to be of a higher histologic grade, such as mucinous or signet ring cell type, and had a greater frequency of developing as multiple synchronous CRCs.

In CD patients, CAC is evenly distributed between the different colonic segments [22].

2.7 Prognosis of CAC

The prognosis for patients with sporadic CRC and CAC is very similar, with 5-year survival rates of 50–60 % [21, 22].

In the study of Watanabe et al. [21], the 5-year overall survival rates of patients with UC-CAC and sporadic CRC were 64.2 % and 68.7 % ($P = 0.585$), respectively. According to Delaunoit et al. [23], 5-year survival rates were 54 % in patients with UC-CAC and 53 % in those with sporadic CRC ($P = 0.94$). However, patients with stage III UC-CAC were shown to have a significantly lower 5-year overall survival rate than those with sporadic CRC (43.3 % vs 57.4 %, $P = 0.032$), whereas the differences for stages I, II, and IV were not significant. Watanabe et al. [21] similarly concluded that the prognosis of patients with advanced-stage UC-CAC is poorer than that of patients with sporadic CRC.

2.8 Molecular Mechanisms of CAC Development

The premalignant lesion→carcinoma sequence of both sporadic CRC and CAC suggests the involvement of multiple gene alterations as the mechanism leading to carcinogenesis [24]. However, CAC differs from sporadic CRC with respect to tumor biology and the pathways leading to malignancy.

Sporadic CRC develops from a premalignant adenoma(s) through mutations in genes such as APC, KRAS (Kirsten rat sarcoma viral oncogene homolog), p53, and DCC (deleted in colorectal carcinoma netrin 1 receptor) [25]. In CAC,

tumorigenesis is via a transition from low- to high-grade dysplasia, although multiple gene alterations are likewise involved [26]. However, there are significant differences in the timing and frequency of the gene alterations leading to sporadic CRC vs CAC.

2.8.1 APC

In sporadic CRC, mutations in the tumor suppressor gene APC have been identified as one of the earliest genetic alterations in the pathogenesis of CRC. APC gene mutations are also found in CAC but generally as much later genetic events.

In the series of Aust et al. [27], one (3 %) out of 30 UC-CAC patients had an APC mutation compared with 11 (26 %) of the 42 patients with sporadic CRC. Similarly, in the study of Tarmin et al. [28], two (6 %) of their 33 patients with UC-associated dysplasia and CAC had a total of three truncating APC mutations compared with 17 (74 %) of the 23 patients with sporadic CRC. The results of these two studies suggest that the loss of APC function is a common initiating event in sporadic CRC but not in CAC.

2.8.2 p53

In sporadic CRC, p53 late-developing mutations are characteristic of morphologically aggressive lesions. Loss of p53 function occurs in approximately 85 % of CAC and is an important step in CAC progression. Mutations in p53 are found not only in dysplastic or malignant cells but also in chronically inflamed nondysplastic mucosa, suggesting that they are an early genetic event in the pathogenesis of CAC [29].

2.8.3 KRAS

KRAS mutations are another early genetic event in the pathogenesis of CAC [30].

2.9 Incidence of CRC in IBD

Table 2.1 summarizes the incidence of CAC in patients with IBD, and Table 2.2 the incidence of CAC and small-bowel cancer in those with CD.

In studies published in the 1980s to 1990s, the risk for CRC in UC was around 7 % 20 years after UC diagnosis [31] and around 14 % at 25 years [32, 33]. In the

Table 2.1 Incidence of colitis-associated cancer in inflammatory bowel disease (IBD)

Author	Year of publication	Type of study	IBD patients	No. of CAC patients	Incidence or risk ratios
Eaden et al. [19]	2001	Meta-analysis	UC	1,698	10 years, 1.6; 20 years, 8.3; 30 years, 18.4 %
Jess et al. [36]	2012	Meta-analysis	UC	229	10 years, <1 %; 15 years, 0.2–2.0 %; 20 years, 1.1–5.3 %
Lutgens et al. [37]	2013	Meta-analysis	UC and CD	NA	10 years, 1 %; 20 years, 2 %; >20 years, 5 %
Ekbom et al. [45]	1990	Population based	UC	91	5.7 (1958–1984)
Winther et al. [34]	2004	Population-based cohort	UC	124	10 years, 0.4 %; 20 years, 1.1 %; 30 years, 2.1 %
Rutter et al. [35]	2006	Prospective	UC	30	20 years, 2.5 %; 30 years, 7.6 %; 40 years, 10.8 %
Lakatos et al. [20]	2006	Population based	UC	13	10 years, 0.6 %; 20 years, 5.4 %; 30 years, 7.5 %
Söderlund et al. [41]	2009	Population based	UC and CD	188	10 years, 1 %; 20 years, 1.5 %; 30 years, 2.7 %
Jess et al. [42]	2012	Nationwide survey	UC and CD	UC: 268, CD: 70	1.34 (1979–1988), 0.57 (1999–2008)
Manninen et al. [43]	2013	Population based	UC and CD	21	1.83 in IBD, 1.99 in UC, 1.82 in CD

CAC, colitis-associated cancer; UC, ulcerative colitis; CD, Crohn's disease; NA, not available

Table 2.2 Incidence of colitis-associated cancer in Crohn's disease (CD)

Author	Year of publication	Type of study	IBD patients	Risk of CAC	Risk of small-bowel cancer
Jess et al. [18]	2005	Meta-analysis	CD	0.9–2.2	3.4–66.7
Canavan et al. [38]	2006	Meta-analysis	CD	2.5	33.2
von Roon et al. [39]	2007	Meta-analysis	CD	2.4	28.4
Laukoetter et al. [40]	2011	Meta-analysis	CD	0.5 person-years	0.3 person-years
Lovasz et al. [44]	2013	Population-based cohort	CD	7.73	NA

IBD, inflammatory bowel disease; NA, not available

early 2000s, the probability of developing CRC in UC was 1.6 % at 10 years, 8.3 % at 20 years, and 18.4 % at 30 years [19]. According to more recent data, the cumulative incidences of CRC in UC are approximately 1.0 % at 10 years, 2.0–5.0 % at 20 years, and 5.0–7.5 % at 30 years [20, 34, 35]. The decreased incidence

of CAC in IBD may be because of the improved therapeutic management of colitis, with higher rates of mucosal healing, but definitive clinical and experimental evidence supporting these observations is lacking.

Because chronic inflammation of the large bowel is an important factor in the development of CRC, anti-inflammatory agents have been considered as chemopreventive agents.

2.9.1 Meta-analysis of the Incidence of CRC in UC

The reported incidence varies widely between studies, which reflects the different periods of data collection, different methodologies, and data originating from studies in different countries. The results of the three meta-analyses published in the English-language literature are summarized briefly below.

Eaden et al. [19] accumulated the results of 116 studies comprising 54,478 patients with UC. In this cohort, there were 1,698 cases of CRC. The probability of developing CRC 10 years after UC diagnosis was 1.6 %, rising to 8.3 % after 20 years and 18.4 % after 30 years. The overall prevalence of CAC in UC in that series was 3.7 %, increasing to 5.4 % in patients with pancolitis. The data pointed to an association between the extent of colitis and the increased risk of CAC.

Jess et al. [36] carried out a meta-analysis of eight studies on the basis of strict inclusion and exclusion criteria. During 14 years of follow-up, 1.6 % of the patients in their study were diagnosed with UC-CAC. The pooled standardized incidence ratio (SIR) was 2.4 (range, 1.05–3.1). The cumulative incidences of CRC development were $<$1.0 % at 10 years, 0.4–2 % at 15 years, and 1.1–5.3 % at 20 years of follow-up. The sex-specific risk ratio was 1.9 in females and 2.6 in males. The age-specific risk ratio was 8.6 in patients 0–39 years of age, 2.1 in those 40–60 years of age, and 1.7 in those 60 years of age and older. Patients with extensive colitis and pancolitis (beyond proctosigmoiditis) had a 4.8-fold higher risk of UC-CAC.

Lutgens et al. [37] reported that the pooled SIR of CRC in IBD patients was 1.7 (range, 1.2–2.2). The cumulative risk of CRC was 1 %, 2 %, and 5 % after 10, 20, and $>$20 years of disease duration, respectively. The authors concluded that the risk of CRC in IBD patients is significantly higher in patients with longer disease duration, extensive disease, and IBD diagnosed at a young age.

2.9.2 Meta-analysis of the Incidence of CRC in CD

In an earlier meta-analysis, Jess et al. [18] evaluated six population-based studies in which the incidence of intestinal malignancies in CD patients was examined. The overall pooled risk estimates (SIRs) for CRCs in CD ranged from 0.9 to 2.2. The SIR for small-bowel cancer ranged from 3.4 to 66.7. The overall pooled estimate for

intestinal malignancies in CD was 27.1. These results showed that CD patients have an overall higher risk of CRC and small-bowel cancer.

Canavan et al. [38] accumulated the results of 13 studies comprising 11,840 patients with CD to examine the incidence of intestinal malignancies in that group. The overall relative risk (RR) of CRC in CD was 2.5 (range, 1.3–4.7). The risk of CRC in CD was shown to be significantly higher than in the general population but not significantly different from that in UC. The cumulative RR for CRC development in CD was 2.9 % at 10 years after CD diagnosis, 5.6 % at 20 years, and 8.3 % at 30 years. However, the authors also found that the overall RR for small-bowel cancer in CD was 33.2 (range, 15.9–60.9). Thus, the risk of small-bowel cancer is much higher in CD patients than in the general population.

Von Roon et al. [39] accumulated the results of 34 studies with a total of 60,122 patients with CD. Compared with the baseline general population, the RRs of CRC and small-bowel cancer were 2.4 (95 % confidence interval, 1.6–4.4) and 28.4 (95 % confidence interval, 14.5–55.7), respectively.

Laukoetter et al. [40] analyzed the results of 20 studies comprising 40,547 patients with CD. The incidence of CD-associated cancer (CDAC) was 0.8/1,000 person-years, meaning that during a 1-year observation period, 0.8 CD patients out of 1,000 developed CDAC. The incidence of CRC and small-bowel carcinoma in CD was 0.5/1,000 and 0.5/1,000 person-years, respectively. The mean age at CRC diagnosis in CD patients was 51.5 years, which is 20 years earlier than in the general population. The mean duration between CD diagnosis and CDAC was 18.3 years.

2.9.3 Incidence of CRC in IBD in a Population-Based Cohort Study

S-derlund et al. [41] assessed cancer occurrence and cancer-related mortality in 7,607 Swedish IBD patients in a population-based cohort study. CRC was detected in 188 IBD patients during 198,227 person-years of follow-up. Compared with the general population, the incidence of CRC in IBD corresponded to an overall twofold higher risk (SIR, 2.3). The overall cumulative incidence of CRC in IBD at 10, 20, and 30 years after IBD diagnosis was 1 %, 1.5 %, and 2.7 %, respectively.

Jess et al. [42] studied CRC risk in a nationwide cohort of 47,374 Danish patients with IBD over a 30-year period. Over the course of the follow-up evaluation, 268 patients with UC (0.5 %) and 70 patients with CD (0.1 %) developed CRC. The overall RR of CRC in UC patients was comparable to that of the general population (RR = 1.1), whereas the RR of CRC in CD patients was slightly lower (0.9) but did not change significantly over time. In UC patients, the overall RR for CRCs decreased from 1.34 between 1979 and 1988 to 0.57 between 1999 and 2008.

Manninen et al. [43] studied the risk of CRC in a nationwide cohort of 1,915 Finnish patients with IBD (1,254 with UC, 550 with CD, and 111 with

inflammatory bowel unclassified). CRC was found in 21 patients. The SIR was 1.83 for IBD, 1.99 for UC, and 1.92 for CD.

Lovasz et al. [44] examined the CRC risk in 640 CD patients with colonic involvement and stenosing disease in a population-based cohort from Hungary. CRC was diagnosed in six CD patients during a follow-up of 7,759 person-years. The mean overall CRC incidence rate was 7.73 per 10,000 patient-years.

2.9.4 Incidence of CRC in UC in a Population-Based Cohort Study

Ekbom et al. [45] examined a population-based cohort of 3,117 patients with UC. In 91 patients with UC, there were 92 cases of CRC (2.9 %). Compared with the general population, the RR for CRC was 1.7 for patients with proctitis, 2.8 for those with left-sided colitis, and 14.8 for those with pancolitis. Less extensive colitis at diagnosis was associated with a lower risk of CRC development.

Winther et al. [34] evaluated a population-based cohort of 1,160 patients with UC in Copenhagen County. After a follow-up of up to 36 years, there were 124 malignancies (10.7 %). The cumulative probability of CRC was 0.4 % by 10 years, 1.1 % by 20 years, and 2.1 % by 30 years of disease. The authors concluded that neither the overall cancer risk nor the risk of CAC was increased after a median of 19 years of follow-up. In their analysis of surgical intervention, the overall cumulative probability of colectomy was 21.3 % after 10 years, 27.9 % after 20 years, 29.9 % after 30 years, and 31.1 % after 35 years. This is in contrast to a rate of 9.1–16.4 % in the cohort reported by Eaden et al. [19]. An active surgical approach after medical treatment failure may explain the low rate of CRC development in the former study.

Rutter et al. [35] examined 600 patients who underwent 2,627 colonoscopic surveillance procedures over a 30-year period, during which 74 patients (12.3 %) developed neoplasia, including 30 cases of CRC (5 %). The cumulative incidence of CRC by colitis duration was 2.5 % at 20 years, 7.6 % at 30 years, and 10.8 % at 40 years. During the surveillance program, 89 patients (14.8 % of the study population) underwent colonic surgery.

Lakatos et al. [20] evaluated the relevant epidemiological and clinical data of 723 UC patients in a Hungarian population-based cohort study. CRC was detected in 13 patients (8,564-person-year duration). The cumulative risk of developing CRC after a 10-year duration of colitis was 0.6 %, which increased to 5.4 % at 20 years and 7.5 % at 30 years.

2.10 Risk Factors for CAC

The increased risk of CAC in IBD patients is thought to be due to genetic and acquired factors (Table 2.3), including the duration, extent, and severity of colitis, the presence of post-inflammatory polyps (pseudopolyps), young age at onset of colitis, sex, family history of sporadic CRC, coexistence of primary sclerosing cholangitis and/or colonic strictures, and the presence of colonic dysplasia. Of these, the most important and well-recognized risk factors for CAC are the duration and extent of colitis.

2.10.1 Duration of Colitis

The importance of colitis duration as a risk factor for the development of CRC in IBD patients is supported by several studies, including the above-cited studies of Eaden et al. [19] (Sect. 2.9.1), Lakatos et al. [20] (Sect. 2.9.4), and Rutter et al. [35] (Sect. 2.9.4). In the study of Lakatos et al. [20], a longer duration of colitis (10 years) was identified as a risk factor for developing CRC, according to a logistic regression model (odds ratio, 8.3; $P = 0.04$). Nieminen et al. [46] examined 183 IBD patients with dysplasia or CRC and 368 matched control patients in a case-control study. They concluded that an increasing degree of inflammation and disease duration cumulatively increased the risk of dysplasia in IBD.

Table 2.3 Risk factors for colitis-associated cancer

Risk factor	Relevant references
Duration of colitis	Eaden et al. [19]; Lakatos et al. [20]; Rutter et al. [35]; Nieminen et al. [46]
Extent of colitis	Ekbom et al. [45]; Eaden et al. [19]; Lakatos et al. [20]; Söderlund et al. [41]; Jess et al. [36]
Severity of colitis	Rutter et al. [47]; Gupta et al. [48]
Post-inflammatory polyps	Rutter et al. [47]; Velayos et al. [49]; Baars et al. [50]
Young age at onset of colitis	Ekbom et al. [45]; Eaden et al. [19]; Jess et al. [36]
Sex	Jess et al. [42]; Ekbom et al. [45]
Family history of sporadic colorectal cancer	Askling et al. [51]; Velayos et al. [49]
Primary sclerosing cholangitis	Broomé et al. [56]; Soetikno et al. [57] Lakatos et al. [20]; Loftus et al. [58]; Nuako et al. [59]
Colonic stricture	Rutter et al. [47]
Colonic dysplasia	Lakatos et al. [20]

2.10.2 Extent of Colitis

Current evidence suggests that the risk of CAC begins to increase after 8–10 years of extensive colitis, defined as left-sided colitis extending from the anal verge to the splenic flexure, and pancolitis (beyond the splenic flexure). By contrast, several studies have shown that there is little or no increased risk of CRC in patients with proctitis or proctosigmoiditis. Chronic colonic inflammation presumably leads to dysplasia and thus eventually to cancer.

The relationship between the extent of colitis and CRC was cited in the abovementioned study of Ekbom et al. [45] (Sect. 2.9.4). In the study of Eaden et al. [19], among UC patients with pancolitis, the cumulative incidence of CRC was 2.1 % at 10 years, 8.5 % at 20 years, and 17.8 % at 30 years disease duration. These data are very similar to the cumulative incidence of CRC in all UC patients, indicating that the development of CRC in UC is associated with pancolitis.

In their univariate analysis, Lakatos et al. [20] showed that patients with pancolitis had a higher risk of CRC than those with left-sided colitis (odds ratio, 5.3; $P = 0.001$). Pancolitis was also identified as a risk factor for CRC development in their logistic regression model (odds ratio, 1.8; $P = 0.04$).

In the above-cited study of Söderlund et al. [41] (Sect. 2.9.3), compared with the general population, the RR of CRC was 2.7 for all UC patients and 5.6 for those with pancolitis. Compared with patients with UC proctitis (RR = 1), the RR of incident CRC was 1.2 for patients with left-sided colitis and 2.0 for those with pancolitis. These data suggest that the greater the extent of colitis, the greater the risk of CRC.

In their meta-analysis (see Sect. 2.9.1), Jess et al. [36] demonstrated that patients with extensive colitis and pancolitis had a 4.8 times higher risk of UC-CAC.

2.10.3 Severity of Colitis

Several reports have demonstrated a significant correlation between the severity of colitis and the risk of CAC, in which chronic inflammation is believed to initiate and promote carcinogenesis in various organs.

Rutter et al. [47] studied 68 patients with CRC and 136 control patients who were matched with respect to sex, extent of colitis, age at diagnosis, duration of colitis, and year of index surveillance colonoscopy. In a multivariate analysis, the authors demonstrated that the histologic severity of colitis was an independent risk factor for the development of CRC (odds ratio, 4.7; $P < 0.001$). A multivariate analysis also showed that a macroscopically normal colonoscopy examination was an independent factor for a lower risk of CRC development (odds ratio, 0.38; $P = 0.003$).

Gupta et al. [48] examined 418 patients with no initial dysplasia who underwent regular endoscopic surveillance. Among them, 15 (3.6 %) progressed to advanced

neoplasia (high-grade dysplasia or colorectal cancer). The authors found a significant relationship between histologic inflammation over time and progression to advanced neoplasia. According to a multivariate analysis, the microscopically determined severity of inflammation was an independent risk factor for developing advanced colorectal neoplasia.

2.10.4 Post-inflammatory Polyps (Pseudopolyps)

Post-inflammatory polyps (colonic pseudopolyps) are irregular islands of colonic mucosa that form by colonic inflammation and regeneration. They are not premalignant lesions and in themselves have no malignant potential. Rather, the presence of post-inflammatory polyps is thought to be a historical marker of previous severe inflammation. As such, they are a known risk factor for CAC.

In the above-cited study of Rutter et al. [47] (Sect. 2.10.3), patients with post-inflammatory polyps had a higher risk of CRC, according to both a univariate (odds ratio, 2.1; $P = 0.006$) and a multivariate (odds ratio, 2.3; $P = 0.005$) analysis.

In a case-control study, Velayos et al. [49] evaluated 188 UC patients with CRC and 188 matched control patients. Based on a univariate analysis, there was a significant association between a prior diagnosis of pseudopolyps and CRC (odds ratio, 2.0; $P < 0.05$), even after adjusting for surveillance colonoscopy and anti-inflammatory therapy (odds ratio, 2.5; $P < 0.05$). These results suggested that a history of post-inflammatory pseudopolyps is a predictive factor for CRC in UC patients.

However, Baars et al. [50] studied the characteristics of IBD-related CRC in a nationwide IBD cohort, in which 251cases of IBD-related CRC were diagnosed (UC, $n = 171$; CD, $n = 77$; unclassified colitis, $n = 3$). The median time from IBD diagnosis to CRC diagnosis was 12 years. Type of IBD, sex of the patient, concomitant PSC, pseudopolyps, extent of inflammation, and medication use were not related to early CRCs that developed within 8 years after the diagnosis of IBD.

2.10.5 Young Age at Onset of Colitis

Young age at colitis onset is recognized as a risk factor for the development of CAC. Ekbom et al. [45] found that the RR of CRC decreased for each increase in age at diagnosis (under 15 years, 15–29 years, 30–39 years, 40–49 years, 50–59 years, and ≥60 years). For patients with extensive disease after 35 years of colitis, the cumulative risk for CRC was 40 % for those diagnosed under the age of 15 years and 25 % for those diagnosed at 15–39 years of age.

Eaden et al. [19] analyzed the incidence of CRC in children diagnosed with UC (average age at UC onset, 10 years). Within this group, the cumulative risk of CRC

was 5.5 % at 10 years, 10.8 % at 20 years, and 15.7 % at 30 years. These rates are higher than the corresponding rates for adults (3 %, 5.9 %, and 8.7 %, respectively).

In the above-cited meta-analysis of Jess et al. [36] (Sect. 2.9.1), the age-specific risk ratio was 8.6, 2.1, and 1.7 in patients 0–39, 40–60, and ≥60 years of age, respectively. Thus, young age at UC diagnosis increased the risk of CRC in UC patients.

2.10.6 Sex

The association between sex and the risk of CRC in IBD has been reported. Jess et al. [36] reported a sex-specific risk ratio of 1.9 in females and 2.6 in males. Ekbom et al. [45] showed a similar risk for IBD-CRC in males and females. Among patients with UC, the RR was 5.6 and 5.9, respectively. In those with CD, the RR was 2.8 and 2.1, respectively.

2.10.7 Family History of Sporadic CRC

Askling et al. [51] assessed the significance of a family history of CRC on the risk of CRC in a population-based cohort study of 19,876 patients with UC or CD. A family history of CRC was associated with a more than twofold risk of CRC (adjusted RR = 2.5). Patients with a first-degree relative diagnosed with CRC before age 50 years also had a higher risk (RR = 9.2).

In the abovementioned case-control study of Velayos et al. [49] (Sect. 2.10.4), a family history of CRC was an independent risk factor for IBD-CRC in patients with UC (odds ratio, 3.7).

2.10.8 Coexistent Primary Sclerosing Cholangitis

Primary sclerosing cholangitis (PSC) is a chronic cholestatic hepatobiliary disease characterized by inflammation and fibrosis of the intrahepatic and extrahepatic biliary tract [52]. PSC causes multiple intrahepatic and extrahepatic biliary strictures, resulting in cholestasis, liver cirrhosis, portal hypertension, and liver failure. Its etiology is thus far unknown, but autoimmunity is thought to be the main cause.

The incidence of IBD in patients with PSC is 25–30 %. However, the association between PSC and CD is relatively rare, such that 85–90 % of the patients with PSC and IBD are those with UC [53].

The association between PSC and CD was first reported by Atkinson and Carroll [54], in 1964, and between PSC and UC by Smith and Loe [55], in 1965. Since then, many studies have identified PSC as a risk factor for the development of CRC in

patients with UC. In the study by Broomé et al. [56], five (28 %) of the 17 UC patients who developed dysplasia or carcinoma had PSC. Soetikno et al. [57] performed a meta-analysis of 11 studies comprising 16,844 patients with UC. Overall, 21 % of the patients with both UC and PSC developed colorectal neoplasms, compared with 4 % of the UC patients without PSC. Among patients with PSC, the RR of developing dysplasia or cancer was 4.8. In both a univariate analysis and a logistic regression model, Lakatos et al. [20] showed that patients with PSC had a higher risk of CRCs (odds ratio, 27.1 and 9.5, respectively). However, these results of an association between PSC and an increased risk of CRC in UC have been contradicted by others [58,59].

2.10.9 Colonic Strictures

In their case-control study of 68 patients with UC and colorectal neoplasia and 136 matched control patients, Rutter et al. [47] found that colonic strictures increased the risk of colorectal neoplasia in UC (odds ratio, 4.62).

2.10.10 Colonic Dysplasia

As noted above, the premalignant histological changes in UC develop from dysplasia rather than adenoma. Adenocarcinoma of the colon develops from a dysplastic precursor lesion. In their univariate analysis and in a logistic regression model, Lakatos et al. [20] showed that patients with dysplasia had a higher risk of CRC (odds ratio, 19.3; $P = 0.0001$ and odds ratio 4.72; $P = 0.05$, respectively).

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Chapter 3
Prevention and Prognosis

Motoi Uchino, Hiroki Ikeuchi, Toshihiro Bando, Kei Hirose, Nobuyuki Hida, and Shiro Nakamura

Abstract Patients with inflammatory bowel disease (IBD) are at high risk of developing colitis-associated colorectal cancer (CA-CRC), and the risk increases with a longer disease duration and is greater in those with continuous inflammation without remission. Thus, surveillance colonoscopy is recommended for patients with IBD because of the rapid progression and extension of CA-CRC, the poor prognosis of patients diagnosed at a younger age, and the higher mortality of CA-CRC than sporadic CRC. Although the efficacy of surveillance for decreasing CA-CRC mortality remains unclear, the early detection of CA-CRC results in a survival rate of these patients similar to that of patients with ulcerative colitis (UC) who develop sporadic CRC. However, UC patients with advanced CRC have a poorer prognosis than non-UC patients with sporadic CRC. In patients with Crohn's disease, surveillance colonoscopy is difficult because of the presence of colonic strictures, such that most CRCs are diagnosed in the advanced stage and the prognosis is worse than in UC or sporadic CRC. Based on the theory of an inflammation-driven carcinogenic process as a causative factor of CA-CRC, treatment for IBD aimed at reducing inflammation may decrease the cancer risk.

Keywords Colitis-associated cancer • Prognosis • Prevention

3.1 Introduction

Patients with inflammatory bowel disease (IBD), which includes ulcerative colitis (UC) and Crohn's disease (CD), are at high risk of developing colitis-associated colorectal cancer (CA-CRC). The risk of CA-CRC increases in IBD patients with a longer duration and greater extent of colitis, continuous inflammation without remission, colitis with backwash ileitis, and primary sclerosing cholangitis [1].

The prognosis of patients with CA-CRC is generally worse than that of patients with sporadic CRC [2–4]. Surveillance colonoscopy is currently recommended by the American Gastroenterological Association, the American College of

M. Uchino (✉) • H. Ikeuchi • T. Bando • K. Hirose • N. Hida • S. Nakamura
Department of Inflammatory Bowel Disease, Hyogo College of Medicine, 1-1, Mukogawacho, Nishinomiya, Hyogo 663-8501, Japan
e-mail: uchino2s@hyo-med.ac.jp

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Gastroenterology, the American Society for Gastrointestinal Endoscopy, and the guidelines for the management of ulcerative colitis in Japan, because patients with CA-CRC typically have a rapid disease progression and extension, a poor prognosis when diagnosed at a younger age, and a higher mortality than those with sporadic CRC [5–12]. Although the efficacy of surveillance in decreasing CA-CRC mortality is unclear, some authors have reported that the early detection of CA-CRS results in a survival rate similar to that of patients with sporadic CRC [13–15]. This chapter addresses the risk factors for CA-CRC, the prognosis of these patients, and the measures aimed at the prevention of CA-CRC.

3.2 Prognosis of Patients with UC and CA-CRC

The factors affecting the prognosis of patients with UC and CA-CRC are not well understood. The cumulative incidence of CA-CRC in UC patients is 2 % after 10 years of disease, 8 % after 20 years, and 18 % after 30 years of disease according to a meta-analysis from 2001 [1]. Previous studies identified several risk factors for CRC in UC, including longer duration and extension of colitis, concomitant primary sclerosing cholangitis, presence of pseudopolyps or backwash ileitis, and a family history of CRC [16–21]. These findings suggest that long-standing and continuous inflammation lead to carcinogenesis, resulting in CA-CRC. Recent studies have suggested that long-term failure to achieve remission from active colitis is a risk factor for CRC, whereas immunomodulators and antitumor necrosis factor were shown to be protective factors [19, 22].

Surveillance colonoscopy for CA-CRC has been largely standardized and is recognized in several guidelines as necessary in patients with long-standing colitis (>8–10 years) in the form of extended pancolitis or left-sided colitis [7–9, 11, 23, 24]. Recent studies have compared the rates of cancer detected at earlier stages (stages I–II) with the CA-CRC rates reported in previous decades [25–27]. A recent study in Japan showed that up to 75 % of CA-CRC patients examined with surveillance colonoscopy were diagnosed with early-stage CRC (stage I or 0) [15].

The first patient with CA-CRC and UC was reported in 1925 by Crohn and Rosenberg, from Mt. Sinai Hospital in New York City [28]. In 1955, before the above-cited predictors were identified and before the concept of surveillance colonoscopy was established, Sugita reported the clinical features and survival of 102 patients with CA-CRC in UC at the same institution [27]. Multiple locations of cancer, high-stage disease, tumors with a high mucin content, or cancer in a flat lesion corresponded to a poor prognosis.

The endoscopic features of CA-CRC, that is, polypoid, nodular, ulcerated, irregular raised lesions, strictures, or plaque-like lesions, resemble those of dysplasia and cancer [29]. However, a flat lesion that may not be detectable by endoscopic biopsy may harbor an underlying invasive cancer [30]. Therefore, such lesions could spread unexpectedly as an advanced cancer even with surveillance colonoscopy. The unexpected spread of cancer may also be understood based on the

epidemiologic and histologic features of these tumors. Poorly differentiated, anaplastic tumors and tumors with a high mucin content are more common in CA-CRC than in sporadic CRC. CA-CRC or dysplasia may be defined as an unequivocal neoplastic alteration of the intestinal epithelium that differs from sporadic cancer [31]. CA-CRC tends to occur in multiple locations and to be of higher histologic grade than sporadic cancer [26]. In particular, there is a higher prevalence of mucinous carcinomas in CA-CRC [26, 32, 33]. A mucinous component occurs in 28 % of cases of CA-CRC [27], whereas in sporadic CRC, mucinous adenocarcinoma accounts for about 10 % of all cases [34, 35]. A recent meta-analysis suggested that mucinous adenocarcinoma has a worse prognosis than typical adenocarcinoma [34–37], although the prognosis of patients with mucinous adenocarcinoma depends on disease stage at surgery [38]. Nonetheless, the 5-year survival rate is significantly worse in patients with than without CA-CRC characterized by a mucinous component (40 % vs. 67 %; $P = 0.03$) [27]. In a comparison of CA-CRC and sporadic CRC, mucinous/signet ring cell carcinoma accounted for 17 % of the cases in CA-CRC vs. 4 % in sporadic CRC [14]. However, a large number of moderately or well-differentiated adenocarcinomas with a small tip of cancer that includes mucinous elements might be accidentally included as a typical adenocarcinoma, which has implications for the prognosis of these patients and may distort the true incidence of mucinous adenocarcinoma.

In view of the histologic findings, in 1976 Riddell et al. [39] suggested a classification that incorporates the features of dysplasia progression and which continues to be largely valid today. The authors classified dysplasia into two common types, adenomatous change and basal cell change, and into three rare types, in situ anaplasia, clear cell change, and pan-cellular change. One of the noteworthy features associated with the deeply invasive behavior of CA-CRC is the mucin component or poorly differentiated adenocarcinoma. If the tip of the tumor is involved, then the disease may extend into the lamina muscularis mucosae without rupturing this layer. Therefore, some deeply invasive CA-CRCs may go undetected during surveillance colonoscopy such that patients may unfortunately be diagnosed only when the disease has reached an advanced stage. Architectural aberrations, such as complex crypt budding, branching, or a back-to-back growth pattern, are also indicative of aggressive dysplasia and CA-CRC.

The efficacy of surveillance colonoscopy for CA-CRC has been evaluated in several studies. In an earlier review article covering the years 1980–1993, among 1916 patients who underwent surveillance colonoscopy, 92 had CA-CRC [40, 41]. Overall, 57 % of the patients were diagnosed with stage A or B disease, according to the Dukes classification, and the remainder with stage C disease. These results together with the incidental detection of CA-CRC during surgery, following barium enema, during sigmoidoscopy, or at the initial colonoscopy of a surveillance program provided strong evidence of the failure of surveillance even in patients with Dukes' A or B disease. Indeed, surveillance was considered to be successful in only 12 % of the cases. With respect to the efficacy of surveillance to detect curable stages of CA-CRC, Choi et al. [42] reported that 19 CA-CRCs (Dukes' A/B/C, 7/8/4) detected by surveillance colonoscopy were found at an earlier stage than

22 CA-CRCs detected without a surveillance program (Dukes' A/B/C, 3/6/13). Furthermore, the 5-year survival rate was higher in the patients with (77.2 %) than in those without (36.3 %) surveillance colonoscopy. Similarly, Connell et al. [43] reported a 5-year survival rate of 87 % for patients with surveillance colonoscopy, compared with 55 % for those without surveillance. In Japan, Hata et al. [13] examined the Dukes' stage of tumors in patients with and without surveillance colonoscopy and reported that four of the five CRCs found in patients undergoing surveillance were stage A, whereas three of the four CRCs in patients without surveillance were stage C. The authors concluded that surveillance is useful for detecting CA-CRC and may contribute to a better prognosis. Fujii et al. [44] analyzed the differences in the depth of cancer invasion, the incidence of lymph node and liver metastases, and the cancer stage in 41 patients with surveillance and 64 patients without surveillance. The results showed that early-stage CRC, defined as within stage T1, was more frequent in patients with than without surveillance (60.5 % vs. 27.6 %, respectively; $P = 0.004$). Patients who had undergone surveillance also had a lower incidence of lymph node metastasis than patients who did not (13.8 % vs. 52.1 %, respectively; $P = 0.002$). Finally, four of the five patients with liver metastasis and all seven of the patients with peritoneal dissemination belonged to the group without surveillance. These findings support the use of surveillance colonoscopy to improve the prognosis of CA-CRC, although surveillance cannot guarantee cancer detection at a curable stage.

With respect to the actual prognosis of CA-CRC, some studies have shown that survival is worse in patients with CA-CRC than in those with sporadic CRC, whereas according to others, survival rates are similar. Ohman et al. [45], from the Karolinska Institutet, Sweden, reported no significant difference in the 5-year survival rate between patients with CA-CRC (47 %, in 29 cases) and those with sporadic CRC (47 %, in 1032 cases). Gyde et al. [46] reported similar 5-year survival rates in a series of patients from West Midlands, England: 33.5 % in the 35 patients with CA-CRC and 32.6 % in the 462 patients with sporadic CRC. In their study from the Mayo Clinic, van Heerden et al. [47] reported that 70 patients with CA-CRC had a worse survival rate than those with sporadic CRC. They also reported that patients with CA-CRC identified incidentally during prophylactic colectomy fared well (72 % 5-year survival rate), while those with clinical symptoms or radiographic suggestion of CRC had a poor 5-year survival rate (35 %). In a report restricted to each cancer stage, Lavery et al. [48], from the Cleveland Clinic, found no significant differences in a stage-matched comparison of 79 patients with CA-CRC and sporadic CRC, although the 5-year survival rate was only 41 % in patients with CA-CRC. In a stage-matched study also from the Mayo Clinic, Delaunoit et al. [26] found similar 5-year survival rates of 53–54 % in 241 patients with CA-CRC and an equal number of those with sporadic CRC. In the recent report of Watanabe et al. [14], the 5-year overall survival rate was similar in 65 patients with CA-CRC and 62,587 patients with sporadic CRC (64.2 % vs. 68.7 %; $P = 0.58$). However, the 5-year survival rate of patients with CA-CRC when grouped according to cancer stage was significantly worse in those with stage 3 disease than in patients with sporadic CRC (43.3 % vs. 57.4 %; $P = 0.03$).

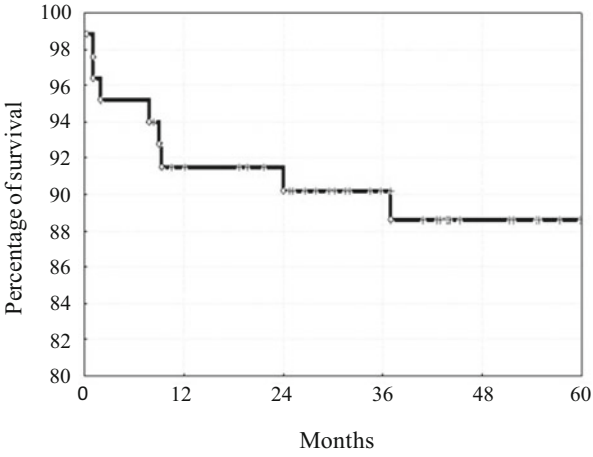

Fig. 3.1 The 5-year overall survival rate in patients with ulcerative colitis–colorectal cancer (UC-CRC). The 5-year overall survival rate was 89 % (Citation from Ref. [15])

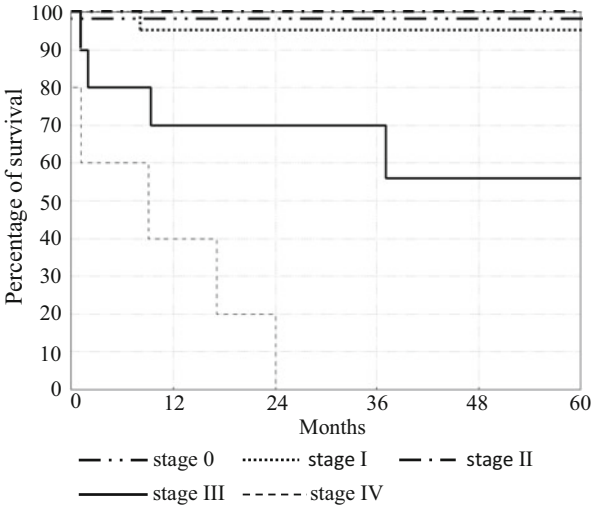

Fig. 3.2 The 5-year survival rates of patients with ulcerative colitis at each stage. Stages 0–II, 100 %; stage I, 96 %; stage III, 56 %; and stage IV, 0 % (Citation from Ref. [15])

Figures 3.1 and 3.2 provide a comparison of cases between January 1984 and December 2010 in patients with CA-CRC; the results are similar to those cited above [15]. In 83 UC patients with CA-CRC, the 5-year overall survival rate was 89 %. The actual 5-year survival rate by stage was 100 % in the 47 patients with stages 0 and II, 96 % in the 21 patients with stage I, 56 % in the ten patients with stage III, and 0 % in the five patients with stage IV [15]. Thus, the prognosis of patients with UC and CA-CRC seems to depend on cancer stage at diagnosis and the pathological features of the tumor.

3.3 Prognosis of Patients with CD and CA-CRC

Unlike in UC, the risk and prognosis of CA-CRC in CD patients are less well validated. Previous studies on the risk of intestinal cancer in CD reported inconsistent results, with relative risk estimates ranging from 0.8 to 20.0 [49]. Previous studies concluded that the predictors of CA-CRC in CD must be evaluated based on the intestinal segment(s) involved by CD, given the different disease behaviors and thus the potential for cancer in the small bowel, colorectal, or anal region.

The risk of CRC in long-standing CD involving the colon is probably comparable to that of UC [2, 3, 50–55]. In a Danish nationwide cohort study, although the relative risk (RR) of CRC in IBD was low in the first years after diagnosis, it was significantly higher than in the background population after a disease duration of 13 years, reaching 50 % [56]. These results are also consistent with the current surveillance guidelines of the American Gastroenterological Association [5] and the British Society for Gastroenterology [57], both of which recommend the initiation of surveillance after 8–10 years of disease duration for CD, as for extensive UC. However, up to a third of IBD patients develop CRC prior to the initial surveillance colonoscopy [56, 58, 59], suggesting the need to reconsider the present surveillance strategy. An additional complicating factor is that the majority of patients with extended colonic CD lesions may require colectomy after a shorter disease duration than is the case in UC patients.

A meta-analysis from 2005 by Jess et al. [60] limited to population-based studies estimated a pooled overall standardized incidence ratio (SIR) for CRC in CD patients of 1.9 [95 % confidence interval (CI), 1.4–2.5]. Separate risk estimates for cancer in the colon and rectum resulted in a significantly higher risk for colon cancer (SIR = 2.5; 95 % CI, 1.7–3.5), while there was no significantly increased pooled risk for rectal cancer (SIR = 1.4; 95 % CI, 0.8–2.6). The risk of CRC was significantly higher in CD patients with colonic involvement (SIR = 4.3; 95 % CI, 2.0–9.4).

The incidence of CRC in CD is similar in Japan and Western countries, but the anatomic location of CRC differs between the respective populations. The study of Jess et al. [60] included populations from North America, Scandinavia, and Israel. Yano et al. [61] found that the SIR for CRC in Japanese patients with CD was 2.79 (95 % CI, 1.28–5.29); in that series, eight of nine patients with CD and CRC had anorectal cancer (ARC). Mizushima et al. [62] also found that the risk of CRC was significantly higher in patients with CD than in the general population (SIR = 5.80; 95 % CI, 2.13–12.68); in their series, five of six patients with CD had ARC. In a review of the Japanese literature, Sugita et al. [63] reported a high incidence (55–89 %) of ARC in patients with CD and CRC. A noteworthy feature of that study was the finding that 55–68 % of the ARC cases involved a colonic stricture without a fistula. In CD, ARC can arise at a similar (or higher) rate in patients with strictures as in those with fistulas. The anatomic location of CRC in CD patients may show racial differences, as suggested by the higher incidence of colonic involvement in Western countries and a higher incidence of anorectal involvement in Asian countries.

With respect to ARC in CD, despite the lack of population-based studies specifically evaluating ARC and although previous studies were from Western countries, it seems that malignancy rarely arises in perianal fistulas [64, 65], but cancer can certainly arise from a long-standing perianal CD fistula [66–68]. Iesalnieks et al. [69] reviewed 23 published reports describing 59 CD patients with adenocarcinoma arising from perianal fistulas. The authors noted that, while the exact pathogenesis of ARC is unclear, the risk of malignant transformation is significantly higher in patients with fistulizing inflammation. They also observed that adenocarcinomas associated with anal fistulas in patients without CD seem to share many features of ARC in those with CD, including a long-term history of perianal fistula (10–20 years) and an increased incidence of mucin-producing adenocarcinomas. Thus, the presence of a long-standing fistula, rather than the disease behaviors of CD itself, seems to be an important predisposing factor for ARC.

Cancer surveillance can be difficult in patients with CD regardless of the anatomic location of either CRC or ARC, because the thoroughness of the examination may be limited by the presence of strictures. Ky et al. [68] suggested that, especially in ARC, carcinoma arising in a CD fistula is very difficult to diagnose, because the examination for anorectal lesions may be limited by pain, stricture, or induration of the perianal and perineal tissues. They noted that although examination under anesthesia can also overlook the lesion, it generally increases the yield of biopsies or curettage of the fistulous tracts. Examination under anesthesia in these cases is also recommended in Japan, but its efficacy has yet to be confirmed [63].

Regardless of differences in the anatomic locations of CRC in different populations, the prognosis of CRC is worse in CD patients than in UC patients. A nationwide population-based cohort study in Denmark [70] established that CD patients with CRC had a significantly worse mortality. Of patients with a history of CD, 62 % died within the first 5 years compared with 56 % of the matched cohort consisting of patients with CRC but without IBD. For CRC patients with CD, the corresponding mortality ratios compared with patients with non-IBD CRC were 1.33 (95 % CI, 1.06–1.66) and 1.26 (95 % CI, 1.07–1.49).

The prognosis of patients with CD and ARC is poor. Igors et al. [69] reported the survival data of 59 CD patients with ARC. The overall survival rates after proctectomy were 88 % at 1 year, 54 % at 3 years, and 26 % at 5 years. Perirectal lymph node metastases were significantly associated with poor outcome ($P < 0.0001$), and all patients with lymph node metastases ($n = 15$) died within 40 months after proctectomy. In a review of the Japanese literature, the overall survival rate after proctectomy was similar: 45 % at 5 years and 30 % at 10 years, even in patients who received postoperative chemotherapy. The overall 5-year survival rate of CA-CRC in 32 patients with CD at our institution between January 1984 and April 2014 was 39.3 % (Fig. 3.3). The patients included three with stage I, 16 with stage II, and six with stage III disease as well as seven patients with an unclassified advanced stage of cancer.

Small bowel carcinoma (SBC) in patients with CD has been discussed controversially. SBC in patients with small bowel CD has long been viewed as a rare and

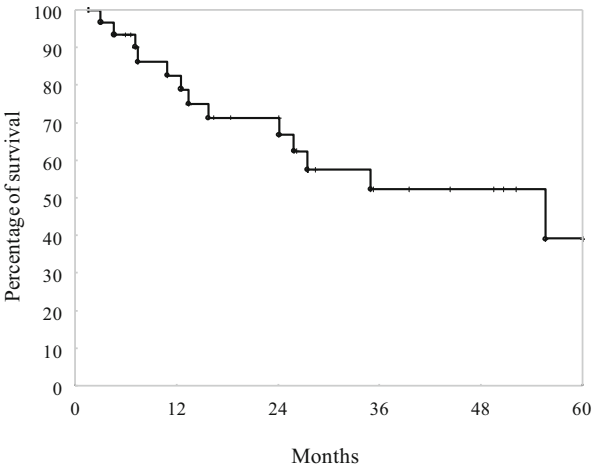

Fig. 3.3 The 5-year overall survival rate of intestinal cancer in patients with Crohn's disease. The overall 5-year survival rate in 32 patients was 39.3 % (Unpublished data at our institution)

ominous disease for which any form of screening or early detection strategy is unlikely to be useful [49]. A meta-analysis from 2005 by Jess et al. [60] found that, although the pooled overall SIR for CRC in CD patients was 1.9 (95 % CI, 1.4–2.5), the SIRs of SBC were not increased either in patients with ileocolonic CD (SIR = 2.6; 95 % CI, 0.8–8.2) or in those with pure jejunoileal disease (SIR = 0.9; 95 % CI, 0.2–4.1). In the meta-analysis of Canavan et al. [49], also published in 2005, analyses of site-specific CD showed no increase in the RR of SBC in the subset of CD patients with ileal disease (RR = 1.1; 95 % CI, 0.8–1.5).

In five previous population-based meta-analyses, the SIR of SBC ranged from 18.75 to 33.2 in patients with CD [49, 60, 70–72]. Jess et al. [60] found that the number of cases of SBC in patients with CD of the small bowel (nine in 26,780 patient-years) was similar to that of CRC in patients with CD of the colon (ten in 32,833 patient-years). In another report based on a hospital cohort of 1935 patients with CD involving the small bowel [73], the cumulative risk of SBC in CD was estimated to be 2 (95 % CI, 0–8) and 22 (95 % CI, 7–64) per 1000 patients after 10 and 25 years of follow-up, respectively. In a recent large, prospective, cohort study of SBC in CD [74], five SBCs were found in 8222 patients with small bowel CD (either alone or associated with colonic CD) during a median follow-up of 35 months (range, 29–40 months). The incidence rates of SBC were 0.235 per 1000 patient-years (95 % CI, 0.076–0.547) among patients with small bowel CD and 0.464 per 1000 patient-years (95 % CI, 0.127–1.190) among those with small bowel CD for 8 years. This accounted for approximately 30 % of the risk of CRC in patients with CD of the colon. Patients with small bowel CD and small bowel CD for 8 years had an SBC SIR of 34.9 (95 % CI, 11.3–81.5) and 46.0 (95 % CI, 12.5–117.8), respectively.

Dossett et al. [75] summarized the features of 154 cases of SBC in CD reported in Europe and America. SBC occurred more frequently in males than in females (M:F = 2.4:1). The age at diagnosis ranged from 21 to 86 years (mean age,

51.3 years), and the average duration of CD was 24.5 years (range, 0–45 years) [75]. CD patients who developed SBC were younger than those with de novo cancers, which occurred mainly in patients 60–69 years of age [76, 77]. Ileal tumors occurred at a rate of 75 %. The presence of tumor in previously bypassed segments of the intestine was 20.3 %. Obstruction was the most common manifestation (76 %), whereas hemorrhage, fistula, and perforation were present in 3.9 %, 3.9 %, and 5.4 % of the cases, respectively. The majority of the diagnoses were made at the time of surgery (35.4 %) or postoperatively (61.5 %). Only 3.1 % of the cases were diagnosed preoperatively.

Thus, patients with CD are also at risk of CA-SBC, albeit the incidence is lower than that of CRC or ARC. However, while the incidence of SBC is low in the general population, it is significantly higher in patients with CD (RR = 27) [78]. Nonetheless, since <1 % of patients with CD will develop SBC and given the similarity of SBC findings and those of CD lesions on some examinations, the diagnosis of SBC in CD patients can be very challenging [79, 80]. Moreover, the prognosis of CD patients with SBC is poor. In the study of Elriz et al. [74], four of the five patients with SBC, diagnosed at an advanced stage by resected specimens, died within 3 years. In the study of Dossett et al. [75], based on 154 cases of SBC in CD reported in Europe and America, the survival rates after 1 and 2 years were 49.6 % and 27 %, respectively. Even in SBC in patients with non-CD, diagnosis was made at a late stage because of limited and insensitive examinations or vague presenting symptoms. Consequently, these patients have a worse prognosis, with a reported 5-year survival of 26 % [81, 82].

In all reports on the incidence of CRC, patients with CD were diagnosed with a more advanced stage of disease than those with UC or no IBD: either Dukes' B or C; stage 3, with lymph node involvement; stage 4; or T2 or T3 with a positive N number [5, 56–59]. Furthermore, in CD, tumors with mucinous components or poorly differentiated adenocarcinomas are not uncommon, even in CA-CRC in CD, regardless of the site of anatomic involvement [26]. In conclusion, the prognosis of CA-CRC in patients with CD may depend on the cancer stage at diagnosis and the pathological features, as in UC; but in patients with long-standing CD, the possibility of concomitant cancer should be considered even in sites of strictureplasty [82–84].

3.4 Chemoprevention of CAC

The results of studies on the risk factors CA-CRC [16–21] suggest that long-standing and continuous inflammation lead to carcinogenesis and in turn CA-CRC. It is also clear that long-term failure to achieve remission from active colitis is a risk factor for CA-CRC [19, 22]. Chronic inflammation may contribute to carcinogenesis by generating a favorable microenvironment for cancer development and progression. Increased concentrations of inflammatory cytokines or mediators, such as reactive oxygen and nitrogen species or cyclooxygenase-2-associated prostaglandins, and alterations of DNA, RNA, proteins, or lipids have

been invoked as events leading to tumor formation. For example, the p53 tumor suppressor gene is mutated in the inflamed mucosa, and expression of the gene was shown to correlate with the intensity of inflammation and with the degree of dysplasia [85]. Thus, it may be that strategies aimed at reducing the inflammation in IBD may also decrease the risk of CA-CRC. Several approaches to achieving this goal are described in the following.

3.4.1 Probiotics

The human gut microflora, comprising some 100 trillion microbial organisms, is critical in maintaining host health, both in the gastrointestinal tract itself and systemically, through the absorption of metabolites [86]. Recent studies have implicated specific strains of bacteria in the regulation of intestinal homeostasis, by delivering regulatory signals to the epithelium, to the mucosal immune system, and to the neuromuscular activity of the gut [87, 88]. However, some commensal and pathogenic organisms belonging to the human enteric microbiome contribute to the pathogenesis of IBD and CRC. Therefore, the use of probiotic bacteria to manipulate gut bacterial composition and local metabolite production has been explored as a therapeutic intervention to prevent CRC. Probiotics are live microbial food supplements with positive effects on host health. However, the efficacy of probiotics in this setting is unclear, and studies in mice have yielded controversial results [88–90]. To date, there have been no proper evaluations in humans.

3.4.2 Aminosalicylate

Patients with IBD are commonly administered 5-aminosalicylate (5-ASA) as maintenance therapy, which in in vitro studies was shown to have antineoplastic properties by inhibiting the nuclear kappa-B pathway involved in tumor progression [91]. However, the evidence for a potential chemoprophylactic effect of 5-ASA is contradictory. In 2005, Velayos et al. [92] reported a meta-analysis of nine studies examining the effect of 5-ASA in preventing CA-CRC in IBD. The pooled analysis revealed a protective effect of 5-ASA use on the risk of CA-CRC (odds ratio = 0.51; 95 % CI, 0.37–0.69). However, a chemopreventive effect of 5-ASA has not been confirmed in case–control and population-based studies [93–95]. In a recent meta-analysis, Nguyen et al. [96] reported a pooled adjusted odds ratio of 0.95 (95 % CI, 0.66–1.38) for CA-CRC in patients with IBD treated with 5-ASA, nor did 5-ASA seem to have a protective effect in preventing CA-CRC in IBD. However, long-standing mild colitis, which could be maintained by 5-ASA administration alone, without aggressive therapy such as corticosteroids, immunomodulators, or biologics, could increase the risk of CA-CRC [15], by maintaining a state of chronic inflammation without complete remission or mucosal healing.

3.4.3 Immunomodulators

An increasing number of IBD patients are being treated with the thiopurine drugs azathioprine and 6-mercaptopurine, based on the consideration that aggressive therapy can induce complete remission and may therefore have a preventive effect. However, data on the potential chemopreventive effect of thiopurines in IBD are conflicting. In the CESAME study [58], nearly half of the 19,484 IBD patients had been exposed to thiopurines; among current users, the adjusted hazard ratio (HR) for CA-CRC was 0.57 (95 % CI, 0.24–1.32), thus ruling out a significant protective effect of thiopurine use on CA-CRC risk in the general IBD population. However, in a subanalysis confined to IBD patients with long-standing extensive colitis, current treatment with thiopurines reduced the risk of advanced CRC significantly (HR 0.28; 95 % CI, 0.09–0.89). In a Dutch cohort study, van Schaik et al. [97] estimated the effect of thiopurines on the risk of CA-CRC in an IBD cohort of 2578 IBD patients, of whom 770 had been exposed to thiopurines. They found that thiopurine exposure decreased the risk of advanced CA-CRC significantly (adjusted HR = 0.10; 95 % CI, 0.01–0.75). However, in a Danish, nationwide, population-based study, Pasternak et al. [98] found no effect of thiopurine on the occurrence of CA-CRC among 43,969 IBD patients, of whom 12 % had been exposed to thiopurines (adjusted RR = 1.00; 95 % CI, 0.61–1.63). Similar results were reported in another large population-based study from the United Kingdom [99].

3.4.4 Biologics

Recent data from models of experimental colitis have demonstrated the tumor-promoting effect of tumor necrosis factor (TNF)-α [100]; but, only a few studies have evaluated the effect of new biological treatments, such as anti-TNF-α, on the risk of CA-CRC, as they have not been used long enough relative to the latency of CA-CRC. In a Dutch nested case–control study, Baars et al. [22] evaluated the risk factors for CA-CRC by comparing 173 CA-CRC patients with 393 non-CRC patients with IBD. They found that the use of anti-TNF-α was a protective factor for the development of CA-CRC (odds ratio = 0.09; 95 % CI, 0.01–0.68). In a Danish nationwide population-based cohort study, the risk of CA-CRC was compared between patients treated or not with anti-TNF-α. There was no correlation between anti-TNF-α and the prevalence of CA-CRC (adjusted RR = 1.06; 95 % CI, 0.33–3.40) [101]. Given that anti-TNF-α may be both tumor promoting and tumor preventing, further studies are needed to confirm its efficacy as a chemopreventive agent.

3.5 Prophylactic Efficacy of Proctocolectomy

3.5.1 Proctocolectomy in Patients with UC

Surveillance colonoscopy for CA-CRC has been standardized, and its use in patients with long-standing IBD (≥8–10 years) has been widely advocated [7–9, 11, 23, 24]. Dysplasia or cancer found in surveillance is an absolute indication for proctocolectomy in patients with UC. Although it remains unclear whether proctocolectomy can decrease the incidence of CA-CRC in UC and improve the prognosis of these patients, the 5-year survival rate was higher in patients who underwent surveillance (87 %) than in those who did not (55 %) [43]. In Japan, Hata et al. [13] suggested that surveillance would allow the detection of CA-CRC at an earlier stage. In a recent review and meta-analysis of the incidence of CA-CRC, the risk of UC patients developing CRC was found to have decreased steadily over the last six decades [102]. Whether these improvements can be attributed to surveillance colonoscopy and prophylactic proctocolectomy remains to be determined.

3.5.2 Proctocolectomy in Patients with Anorectal CD

In patients at risk of SBC, prophylactic resection of the small intestine is contraindicated by its absolute necessity for nutrient absorption, although total parenteral nutrition therapy can be considered. However, in patients with anorectal CD, prophylactic proctectomy may decrease the incidence of ARC. As discussed in Sect. 3.3, ARC is rarely detected in its early stage owing to the difficulty of proper surveillance and accurate diagnosis. Furthermore, ostomy diversion of anorectal CD increases the risk of ARC [64, 65, 69]. However, in patients with severe perianal disease with stricture, in whom both medical management and local surgical treatment have failed, the first surgical option is a diverting colostomy or ileostomy. If these do not provide sufficient relief, the final option is proctectomy, performed in 10–20 % of patients with perianal CD [103, 104]. Proctectomy generally consists of either a low Hartmann's procedure or a complete proctectomy with sphincter resection. The disadvantages of Hartmann's procedure include the risk of ARC in the residual distal rectum. This can cause persisting complaints of Crohn's disease, and anastomotic breakdown will result in a presacral abscess draining and fistulizing through the perineum [105–108]. Therefore, in our institution, complete proctectomy is preferred when the stricturing anorectal lesion, regardless of the presence of a fistula tract, cannot be improved by any treatment. In our experience, proctectomy for these lesions improves not only the severe symptoms of anorectal lesions but also the incidence of ARC. However, an as yet unresolved problem is that the perineal wound after proctocolectomy heals poorly and there is a high incidence of persistent sinus in patients with CD [109, 110]. Long-term cohort studies, performed after several decades, are still needed to determine the outcomes of these patients.

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Part II
Diagnosis

Chapter 4
Cancer Surveillance of Patients with Long-Standing Inflammatory Bowel Disease

Yoshiki Okita, Toshimitsu Araki, Koji Tanaka, Yuji Toiyama, Keiichi Uchida, and Masato Kusunoki

Abstract In response to the recognition of the higher risk of cancer in patients with inflammatory bowel disease (IBD), surveillance for those with long-standing disease has become an important tool in detecting and treating neoplastic lesions at an early stage and thus in the reduction of colitis-associated mortality. Most of the recent guidelines agree on the following: (1) For patients with proctosigmoiditis, a regular screening or surveillance colonoscopy program for detecting CRC is not necessary. (2) Surveillance colonoscopy should be started 6–10 years after the onset of symptoms for patients with left-sided or extensive colitis. (3) Ongoing surveillance colonoscopy should be carried out based on the individual risk profile. (4) Two to four random biopsy specimens should be taken every 10 cm along the entire colon, with additional samples acquired in suspicious areas. The random biopsy is now increasingly criticized because of its low yield in detecting neoplasia. In several guidelines, chromoendoscopy with targeted biopsies is an acceptable alternative to white light endoscopy with random biopsy. The value of other newer endoscopic techniques such as narrowband imaging, autofluorescence imaging, and fluorescence endoscopy, with targeted biopsies, remains to be determined.

Keywords Surveillance • Random biopsy • Targeted biopsy • Chromoendoscopy

4.1 Introduction

Crohn first described colorectal cancer (CRC) in association with inflammatory bowel disease (IBD) in 1925 [1]. Since then, the association between ulcerative colitis (UC) and carcinoma of the colon has been confirmed in numerous studies [2–5]. However, concerns remain regarding the adequate surveillance, diagnosis, and treatment of early preneoplastic and neoplastic lesions [6].

Y. Okita (✉) • T. Araki • K. Tanaka • Y. Toiyama • K. Uchida • M. Kusunoki
Department of Gastrointestinal and Pediatric Surgery, Mie University Graduate School of Medicine, 2-174 Edobashi, Tsu, Mie 514-8507, Japan
e-mail: nyokkin@clin.medic.mie-u.ac.jp

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UC is a well-characterized chronic idiopathic form of IBD. The long-standing nature of UC and its relapsing and remitting course carry an increased risk for the development of colorectal neoplasia [7]. The overall prevalence of CRC in any UC patient was estimated to be 3.7 % in a large meta-analysis reported by Eaden et al. in 2001 [8]. Patients with a course of disease longer than 10 years and those with pancolitis are at the highest risk. Compared with the general population, patients with left-sided UC or those with more proximal disease are considered to be at greater risk for cancer development [9, 10].

Recent data have shown that colitis of Crohn's disease (CD) carries a similar magnitude of risk for the same disease extent. Canavan et al. [11] reported that the cumulative risk for patients with CD was 2.9 % at 10 years, 5.6 % at 20 years, and 8.3 % at 30 years after CD diagnosis and that, following a diagnosis of CD, the cumulative risk of developing CRC is comparable to the risk associated with UC [11].

Given the higher risk for cancer development, surveillance in patients with long-standing IBD has become an important tool in detecting and treating neoplastic lesions at an early stage and thus in the reduction of colitis-associated mortality [12]. Various guidelines, such as those of the European Crohn's and Colitis Organisation (ECCO), British Society of Gastroenterology (BSG), and American Gastroenterological Association (AGA), have been introduced to improve the detection of dysplasia and the management of surgically curable cancer and thereby the prognosis of these patients. This chapter provides a review of the current status of neoplasia surveillance in patients with long-standing IBD.

4.2 Risk Factors for Colitis-Associated Cancer in UC (Table 4.1)

Based on the long-term follow-up reported in a subset of the studies included in the meta-analysis by Eaden et al. [8], the cumulative risk of CRC in patients with left-sided disease or pancolitis was 1.6 % at 10 years, 8.3 % at 20 years, and 18.4 % at 30 years after the development of UC [8]. Several studies have shown a general consensus regarding little or no increased risk of CRC in patients with proctitis or proctosigmoiditis, an intermediate risk in those with left-sided colitis, and the highest risk in those with pancolitis. The meta-analysis by Eaden et al. [8] also reported an overall prevalence of 3.7 % for CRC among patients with UC in all 116 studies; however, when the analysis was restricted to the 35 studies that stratified their own analyses by extent of UC, the prevalence of CRC among patients with extensive involvement rose to 5.4 % [8, 13]. Disease duration and anatomic extent are well-established risk factors for the development of CRC.

Determination of anatomic extent in assessing cancer risk has historically been based on macroscopic rather than histologic inflammation. Both macroscopic and microscopic healing may occur, but once extensive colitis is documented, an

Table 4.1 Risk factor for colitis-associated cancer for ulcerative colitis

Extensive colitis
Primary sclerosing cholangitis
Severe long-standing inflammation
Inflammatory polyps
Colonic stricture
Family history of colorectal cancer, especially aged <50
Personal history of dysplasia

increased risk of cancer should be assumed depending on the greatest previously determined extent. Mathy et al. [14] reported that colitis-associated cancer in patients with UC may arise in endoscopically normal but histologically involved areas of the colon. They concluded that further studies are needed to determine the risk of colitis-related neoplasia in patients with microscopic pancolitis but limited gross disease.

A study from the Netherlands suggested that cancers will be missed if surveillance is commenced at 8–10 years for patients with pancolitis and at 15–20 years for patients with left-sided disease because 9–15 % of the cancers that developed in their study patients occurred before these time frames [15]. Indeed, up to 22 % of patients who develop a colitis-associated colon carcinoma do so prior to commencing surveillance colonoscopies. However, the majority of studies have shown that the incidence is very low at 10 years of disease, and might even be decreasing [8, 16–18].

The wide variation of risk estimates reported in the literature may be attributed to differences in additional risk factors in the patient cohorts studied. The most consistent risk factor reported is primary sclerosing cholangitis (PSC), which corresponds to a CRC risk up to 31 % [19–21]. Soetikno et al. [22] conducted a meta-analysis of 11 studies and found that, overall, 21 % of the patients with both UC and PSC developed colorectal neoplasms, compared with 4 % of the patients without PSC.

Histologic or clinical disease activity is regarded as a risk factor for colitis-associated cancer [7, 23, 24]. Postinflammatory polyps may be markers of previous inflammatory severity and are closely related to the neoplasm [7, 25, 26]. A case-control study of patients with UC from St. Mark's Hospital demonstrated that inflammatory polyps and colonic strictures increased the risk of CRC by twofold and fourfold, respectively, compared with individuals without these abnormalities [27]. In addition, a population-based cohort study reported that a family history of CRC was associated with a more than twofold higher risk of IBD-associated CRC [adjusted relative risk (RR) = 2.5; 95 % confidence interval (CI), 1.4–4.4]; furthermore, patients with a first-degree relative diagnosed with CRC before 50 years of age also had a higher risk (RR = 9.2; 95 % CI, 3.7–23) [28]. According to these data, the surveillance strategy for a particular patient should be determined based not only on the duration and extent of colitis but also on the presence of other risk factors.

4.3 Incidence and Prevalence of CD-Associated Cancer

Because of the chronic intestinal inflammation characteristic of the disease, CD is regarded as a risk factor for intestinal carcinoma. However, while some studies have reported that CD patients have an increased risk of cancer [29–35], other studies did not find any correlation [36–39]. In their 1994 study of the CRC risk in CD in a cohort of 281 patients, Gillen et al. [32] showed that those with extensive CD-associated colitis had an 18-fold higher risk, which decreased with increasing age at onset but increased significantly with a young age at onset.

A Canadian cohort study matched a population-based IBD database to a cancer registry in North America between 1984 and 1997 [34]. The incidence of CRC was higher in those with Crohn's colitis (RR = 2.64; 95 % CI, 1.69–4.12) or UC (RR = 2.75; 95 % CI, 1.91–3.97) than in the general population. That study also found a higher risk of rectal cancer in patients with UC (RR = 1.90; 95 % CI, 1.05–3.43) but not in those with Crohn's colitis (RR = 1.08; 95 % CI, 0.43–2.70).

Previous studies reported an increased risk of cancer in patients with CD of longer duration and extent [40, 41]. Stahl et al. [40] showed that patients with an early onset of CD were at higher risk for developing cancer; according to Maykel et al. [41], advanced age at CD diagnosis increased the risk of developing cancer [40, 41].

In the meta-analysis by von Roon et al. [42], based on 34 studies comprising 60,122 patients with CD, the RR of small bowel cancer or CRC compared with the baseline population was 28.4 (95 % CI, 14.46–55.66) and 2.4 (95 % CI, 1.56–4.36), respectively. In a subgroup analysis, patients with CD had an increased risk of colon cancer (RR = 2.59; 95 % CI, 1.54–4.36) but not of rectal cancer (RR = 1.46; 95 % CI, 0.8–2.55) [42].

The meta-analysis of Laukoetter et al. [43] consisted of 20 clinical studies with a total of 40,547 patients. The incidence of CD-associated cancer in CD patients was 0.8/1,000 person-years, meaning that during a 1-year observation period, 0.8 CD patients out of 1,000 developed CD-associated cancer. CD-associated CRC had a pooled incidence of 0.5/1,000 person-years (95 % CI, 0.3/1,000–0.6/1,000 person-years). The prevalence was 0.24 % (95 % CI, 0.19–0.28). The incidence of CRC and small bowel carcinoma in CD was 0.5/1,000 and 0.5/1,000 person-years, respectively. The pooled incidence of carcinomas in patients with fistulas was 0.2/1,000 person-years (95 % CI, 0.0/1,000–0.4/1,000 person-years). The mean duration between CD diagnosis and CD-associated cancer was 18.3 years. The authors concluded that although the risk of CRC is significantly increased in patients with CD, it is far lower than in those with long-standing UC. However, this meta-analysis did not find a significant relationship between cancer development and either the anatomic segments involved by CD or longer disease duration, although in the latter there was a trend toward a higher incidence. A stratification of cancer risk by disease duration has not been possible because of the paucity of appropriate studies [11].

Moreover, the benefit of surveillance colonoscopy in CD has yet to be established, and the early detection of small bowel carcinoma in patients with CD remains problematic. Routine magnetic resonance enteroclysis/enterography or capsule endoscopy could potentially detect these malignancies at an early stage, but the use of these methods to screen asymptomatic individuals is costly and has not been shown to prolong survival in patients with CD.

4.4 Timing of Initial Screening Colonoscopy and Surveillance Interval in Patients with UC (Table 4.2)

Most of the recent guidelines agree on the following: (1) For patients with proctosigmoiditis, regular screening or surveillance colonoscopy for detecting CRC is not necessary. (2) Surveillance colonoscopy should be started 6–10 years after the onset of symptoms for patients with left-sided or extensive colitis. (3) Ongoing surveillance colonoscopy should be carried out based on the individual risk profile.

There are some minor variations among the guidelines with respect to the timing of initial screening colonoscopy and the surveillance interval. In the guidelines of both the ECCO and the BSG, initial screening and surveillance colonoscopy for detecting CRC are determined based on risk stratification. The 2013 guideline of the ECCO recommends that patients with extensive UC as well as those with left-sided UC who have at least 8 years of disease beginning from the onset of symptoms should undergo screening colonoscopy. The ECCO's recommendations for surveillance colonoscopy are cited below [44]:

1. In all patients with UC irrespective of the disease activity, a screening colonoscopy could be carried out 6–8 years after the beginning of symptoms to assess the patient's individual risk profile.
2. When disease activity is limited to the rectum without evidence of previous or current endoscopic and/or microscopic inflammation proximal to the rectum, inclusion in a regular surveillance colonoscopy program is not necessary.
3. In cases with concurrent primary sclerosing cholangitis (PSC), surveillance colonoscopies should be carried out yearly from the point of PSC diagnosis irrespective of disease activity and extent.
4. The CRC risk profile should be determined at the screening colonoscopy or the first surveillance colonoscopy 6–8 years after the first manifestation. Risk stratification mainly depends on extent of disease, severity endoscopic and/or histological inflammation, pseudopolyps, concurrence of PSC, and family history of CRC.
5. The individual risk profile dictates surveillance colonoscopy intervals: every 1–2 years (high risk) or every 3–4 years (low risk) from the eighth year after the first manifestation in both extensive UC and left-sided UC.

Table 4.2 Comparison of screening recommendation from international guidelines for patients with colitis

	ECCO 2013	BSG 2010	AGA 2010	ACG 2010
First screening	6–8years	10 years	Maximum 8 years	8–10 years
Surveillance interval	High risk, 1–2 years	High risk, 1 year	1–3 years	8–10 years
	Low risk, every 3–4 years	Intermediate risk, 3 years	More often at high risk	1–2 years
			E.g., PSC	
		Low risk, every 5 years		
Biopsy	Targeted biopsy with chromoendoscopy by trained endoscopist	Targeted biopsy with chromoendoscopy is recommended.	Random biopsy ($\geq$33) from each anatomic section	Multiple biopsies at regular intervals
	Quadrant biopsies every 10 cm	Two to four biopsies every 10 cm if no chromoendoscopy	Targeted biopsy with chromoendoscopy by trained endoscopist	Targeted biopsy with chromoendoscopy by trained endoscopist

ECCO European Crohn's and Colitis Organisation; *BSG* British Society of Gastroenterology; *AGA* American Gastroenterological Association; *ACG* American College of Gastroenterology; *PSC* primary sclerosing cholangitis

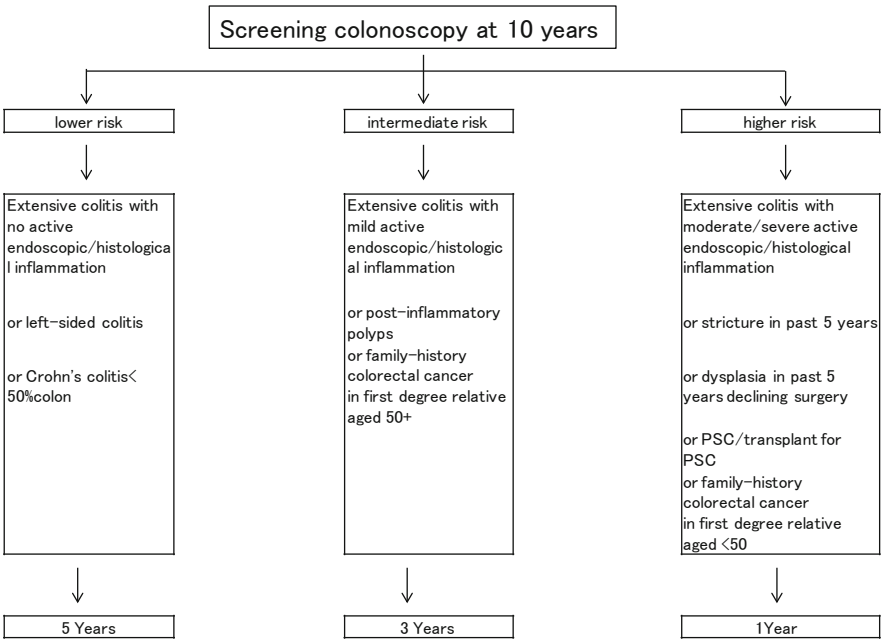

Fig. 4.1 Surveillance recommendations for patients with colitis from the British Society of Gastroenterology

In the BSG guideline, the surveillance colonoscopy program is decided upon based on the individual risk profile (Fig. 4.1). Screening colonoscopy and surveillance colonoscopy are recommended as follows [45]:

1. All patients with UC or Crohn's colitis should undergo a screening colonoscopy approximately 10 years after the onset of colitis symptoms to assess disease extent and other endoscopic risk factors.
2. Surveillance colonoscopies should be performed, where possible, when the disease is in remission. Surveillance procedure should not be unduly delayed if remission cannot be achieved.
3. The risk of cancer is influenced by the duration and extent of disease and additional risk factors (such as PSC and family history of CRC) and is also linked to the endoscopic and histologic appearances at colonoscopy.
4. If a dysplastic polyp is detected within an area of inflammation and can be removed in its entirety, it is not necessary to recommend colectomy.

According to the BSG, surveillance intervals are determined according to risk category (higher risk, yearly; moderate risk, every 3 years; higher risk, every 5 years).

The 2010 guideline of the AGA recommends that all patients, regardless of the extent of disease at initial diagnosis, undergo a screening colonoscopy at a

maximum of 8 years after the onset of symptoms [46]. The AGA's recommendations for screening colonoscopy and surveillance colonoscopy are as follows:

1. All patients, regardless of the extent of disease at initial diagnosis, should undergo a screening colonoscopy a maximum of 8 years after onset of symptoms, with multiple biopsy specimens obtained throughout the entire colon, to assess the true microscopic extent of inflammation.
2. Patients with ulcerative proctitis or ulcerative proctosigmoiditis are not considered at increased risk for IBD-related CRC and thus may be managed on the basis of average-risk recommendations.
3. Patients with extensive or left-sided colitis, with a negative screening colonoscopy, should begin regular surveillance colonoscopy within 1–2 years.
4. After two negative examinations (no dysplasia or cancer), further surveillance examinations should be performed every 1–3 years. Increasing the frequency of surveillance colonoscopy to every 1–2 years after 20 years of disease is not needed for all patients but should be individualized according to the presence or absence of other risk factors.
5. Patients with PSC should begin surveillance colonoscopy at the time of this diagnosis and then undergo yearly colonoscopy thereafter.
6. Patients with a history of CRC in first-degree relatives, ongoing active endoscopic or histologic inflammation, or anatomic abnormalities such as a foreshortened colon, stricture, or multiple inflammatory pseudopolyps may benefit from more frequent surveillance examinations.

The 2010 American College of Gastroenterology guideline recommends that initial screening should be started after 8–10 years of colitis in patients with either left-sided colitis or pancolitis and annual or biannual surveillance should be performed [47].

The 2006 guideline for the management of UC in Japan recommends that surveillance colonoscopy should be started 8–10 years after disease onset for patients with extensive colitis and annual or biannual colonoscopy, including biopsies, beginning 8–10 years after disease onset in patients with extensive colitis [48]. In this guideline, surveillance colonoscopy for detecting CRC is not determined based on risk stratification.

4.5 Sampling Method: Step Biopsy or Target Biopsy? (Table 4.2)

While surveillance colonoscopy allows the early detection and treatment of CRC, especially in patients with long-standing UC, the flat or diffuse infiltrative macroscopic lesions that sometimes arise in UC are difficult to see endoscopically. In their 1986 study, Broström et al. [49] examined the use of surveillance colonoscopy for the early detection of dysplasia. The entire colon was separated into ten segments, and two biopsies were taken at each one. Manning et al. [50] reported the results of a prospective study of screening for colorectal epithelial dysplasia by regular

colonoscopy. In their 1987 study, biopsy specimens were taken from flat mucosa at approximately 8–10-cm intervals along the colon and rectum and from any identifiable mass lesions. Based on these and other studies of surveillance colonoscopy, the practice of multiple biopsies in patients with long-standing UC during surveillance colonoscopy has been widely adopted.

Rubin et al. [51] used a mathematical model to show that 33 biopsy specimens were needed to detect dysplasia with 90 % probability, if dysplasia is present. At least 64 biopsy specimens were needed to reach a 95 % probability of detecting dysplasia. That study provided the basis for surveillance practice recommendations. Current guidelines for dysplasia surveillance recommend quadrant-based random biopsies every 10 cm throughout the entire colon and a minimum of 33 biopsies [44–47]. However, random biopsy samples only 0.03 % of the mucosal surface, has a detection rate of <2 per 1,000 biopsies [52], and does not affect clinical decision-making when advanced techniques are used [53]. Broek et al. [52] retrospectively analyzed 466 surveillance colonoscopies (in 167 patients) during which 11,772 random biopsies were obtained. The authors concluded that the low yield and lack of clinical consequences from random biopsies question its necessity and cost-effectiveness in UC surveillance. Thus, chromoendoscopy (CE) provides an alternative to colonoscopy with random biopsies, and its use is supported in recent guidelines [44, 45].

Moreover, recent data have shown that most gastroenterologists do not follow the recommended biopsy protocol. In a study from the Netherlands, only 27 % of gastroenterologists complied with the recommended number of 33 random biopsies [54]. Eaden et al. [55, 56] used a questionnaire to show that >50 % of the gastroenterologists surveyed obtained fewer than ten colonic mucosal biopsies per endoscopic surveillance examination.

The BSG guideline recommends pancolonic dye spraying with the targeted biopsy of abnormal areas; otherwise, two to four random biopsy specimens from every 10 cm of the colorectum should be taken, with additional biopsies of suspicious areas.

The Research Group of Intractable Inflammatory Bowel Disease of the Ministry of Health, Labour and Welfare of Japan is carrying out a randomized controlled study to compare the efficacy of step biopsy and target biopsy [57]. The results of this study will soon be available.

4.6 Chromoendoscopy and Other Newer Endoscopic Techniques

4.6.1 Chromoendoscopy

Target biopsy techniques have gained increasing acceptance [58]. Among these newer techniques CE is the most well established, and it has been used to better define the superficial gastrointestinal mucosa [59]. CE involves the topical

application of a dye onto the colonic mucosa. It has two main advantages [27]: (1) it improves the detection of subtle colonic lesions, which raises the sensitivity of the endoscopic examination, and (2) once a lesion is detected, its CE appearance can aid in its characterization, which raises the specificity of the endoscopic examination [46, 56]. Previous studies demonstrated that the use of CE increases the detection rate of dysplasia by two- to threefold, corresponding to a per lesion increase of four- to fivefold [60–62].

Use of a magnifying colonoscope may further increase the sensitivity and specificity of CE [46]. Crypt architecture can be categorized by evaluating the pit pattern, which aides in the differentiation between neoplastic and nonneoplastic changes and in the performance of targeted biopsies [63].

The different stains used in CE can be classified as absorptive or contrast agents [59]. Absorptive agents include methylene blue (0.1–0.5 %) and cresyl violet (0.2 %). They are rapidly absorbed by normal colonic mucosa but poorly absorbed by dysplastic or inflamed tissue, thus enhancing the superficial structure of lesions and demonstrating the various cell types. Contrast agents, such as indigo carmine, pool in the mucosal grooves without reaction and absorption and thus highlight the superficial structure of lesions.

Several studies have evaluated the use of CE as an adjunctive method to diagnose dysplasia or cancer, based on its ability to more accurately evaluate the extent of disease and the degree of inflammatory activity [60, 62, 64–66]. In the study of Kiesslich et al. [64], patients with long-standing UC were assigned to conventional colonoscopy or colonoscopy with CE using methylene blue. The correlation between the endoscopic assessment of both the degree and the extent of colonic inflammation was better in the CE group than in patients examined with conventional colonoscopy. In addition, more targeted biopsies were possible with CE, and significantly more dysplasia was detected. The sensitivity and specificity for the differentiation of nonneoplastic from neoplastic lesions were both 93 %.

In a randomized control study, Rutter et al. [60] evaluated 100 patients with long-standing extensive UC who underwent “back to back” colonoscopies with both random and targeted biopsies, followed by spraying with indigo carmine and biopsies. Median extubation times for the first and second colonoscopies were 11 and 10 min, respectively. During conventional colonoscopy, 43 mucosal abnormalities were detected, of which two were dysplastic. Following dye spraying, 114 additional abnormalities were detected, of which seven were dysplastic. The targeted biopsy protocol detected dysplasia in significantly more patients than achieved with the nontargeted protocol [60].

Hurlstone et al. [66] analyzed 350 patients with long-standing UC who underwent surveillance colonoscopy using high-magnification CE. Quadrant-based biopsies at 10-cm intervals were taken on extubation, in addition to targeted biopsies of abnormal mucosal areas. The data were compared to those from 350 control patients, matched for disease duration and extent, who had undergone conventional colonoscopic surveillance. Significantly more intraepithelial neoplastic lesions were detected in the magnification chromoscopy group than in the controls (69 vs. 24 lesions, $P < 0.0001$). In addition, a greater number of flat lesions

with intraepithelial neoplasia were detected in the CE group than in controls (53 vs. 14 lesions, $P < 0.001$). The authors concluded that magnification CE can predict neoplastic and nonneoplastic mucosal changes with a high overall accuracy [66].

4.6.2 Virtual Chromoendoscopy

Newer endoscopic techniques are being explored to aid in the diagnosis of dysplasia in IBD, although none has yet been rigorously studied. These new techniques include virtual chromoendoscopy (VCE), narrow band imaging (NBI) [67], fluorescence endoscopy [68, 69], optical coherence tomography [70], and confocal endomicroscopy [61, 70, 71].

VCE, also called dye-less chromoendoscopy, is a recently developed imaging technique that comprises NBI (Olympus, Tokyo, Japan), Fujinon intelligent color enhancement (FICE; Fujinon, Tokyo, Japan), and i-Scan (Pentax, Tokyo, Japan). NBI provides clear imaging of the microvascular structure of the colon. Its development was motivated by the quest for a simpler technique that would obviate the complexity of CE [67]. This unique form of electronic CE was first described by Gono et al. [72]. The method is based on illumination of the mucosal surface by light with a defined narrow band of wavelengths. Two narrow bands, centered at 415 (blue light) and 540 nm (green light), are used in the system introduced by Olympus (Olympus Medical, Tokyo, Japan). These selected wavelengths can pass through the mucosa to a defined depth, and their absorption correlates with the absorption maximum of a molecule of hemoglobin. A wavelength of 415 nm penetrates only the very superficial layers of the mucosa and is absorbed by blood in the intrapapillary capillary loops. The narrow band centered at 540 nm penetrates the deeper level and accentuates the venules and arterioles located under a layer of intrapapillary capillary loops. Using NBI to illuminate the mucosal membrane substantially increases the contrast between blood-containing vessels and the surrounding tissues, allowing even very subtle changes in the microvascular architecture to be identified [73].

Dekker et al. [67] carried out a prospective, randomized, crossover study of 42 patients with long-standing UC and compared the accuracy of NBI with that of standard colonoscopy for the detection of neoplasia. Using NBI, 52 visible lesions were identified in 17 patients, whereas with standard WLE, 28 lesions were detected in 13 patients. Pathologic evaluation of targeted biopsies identified 11 patients with neoplasia. Neoplasia was detected by both techniques in four patients but only by NBI or conventional colonoscopy in four and three patients, respectively. The sensitivity of that first-generation NBI system for the detection of neoplasia was comparable to that of conventional colonoscopy, although a larger number of suspicious lesions were found during NBI. The authors concluded that it is still too early to stop taking additional random biopsies at surveillance colonoscopy in patients with UC [67].

Two other trials demonstrated that high-definition WLE was equivalent to NBI [74, 75]. In the study of van den Broek et al. [74], 11 out of 16 (69 %) neoplastic lesions were detected by high-definition WLE and 13 out of 16 by NBI (81 %) ($P = 0.727$). In the study of Ignjatovic et al. [75], there was no difference in the proportion of patients with at least one area of dysplasia detected by WLE vs. by NBI, with five patients having at least one dysplastic lesion in each group [odds ratio (OR) = 1.00; 95 % CI, 0.27–3.67; $P = 1.00$]. This remained unchanged when adjusted for other variables (OR = 0.69; 95 % CI, 0.16–2.96; $P = 0.62$).

Efthymiou et al. [76] evaluated 44 patients with IBD to compare CE and NBI with respect to lesion detection and to assess the accuracy of the mucosal pit pattern (Kudo classification) as seen on NBI in predicting mucosal histology. CE identified more lesions than NBI (131 vs. 102, $P < 0.001$), detecting 23 neoplastic (dysplastic or indefinite for dysplasia) lesions in 11 patients compared with the 20 lesions in 10 patients detected by NBI ($P = 0.180$). Kudo classification by NBI had a low sensitivity and modest accuracy for dysplasia (42 % and 74 %, respectively). The authors concluded that there was a nonsignificant trend in favor of CE for the detection of dysplasia and that NBI cannot be recommended as an alternative to CE for dysplasia surveillance [76].

Pellisé et al. [77] examined the number of false-positive and true-positive lesions in patients undergoing CE and NBI as well as the proportion of patients with missed intraepithelial neoplasia lesions. In the per-lesion analysis, NBI had a significantly lower false-positive biopsy rate ($P = 0.001$) and a similar true-positive rate [77]. The efficacy of NBI in the endoscopy-based differential diagnosis of sporadic neoplasia vs. colitis-associated dysplasia or cancer remains to be confirmed [78].

4.6.3 Autofluorescence Imaging

Autofluorescence imaging (AFI) is a novel technique that takes advantage of the fluorescence of tissues exposed to ultraviolet (<400 nm) or short-wavelength visible (mostly blue) light. The autofluorescence produced by certain molecules (fluorophores) has a longer wavelength than that of the excitation light [59, 79]. Tissue autofluorescence is influenced by several factors, including the architecture and light absorption properties of the tissues (the latter is mainly determined by the concentration of hemoglobin in the tissues), their biochemical environment, and their metabolic status [59, 80]. These features are distinct in neoplasia, as the greenish background of normal colonic tissue is replaced by a purple-colored mucosa [59].

In their prospective pilot trial ($n = 50$) using a randomized crossover design between standard targeted WLE biopsies and AFI-targeted biopsies, van den Broek et al. [81] demonstrated significantly better detection in the AFI-first group, in which ten neoplastic lesions were detected among 25 patients, while WLE did not detect any additional lesions. In the WLE-first group, three lesions were detected among 25 patients, and subsequent AFI detected three more ($P = 0.036$). This study

reported that the Kudo classification by NBI had a sensitivity and specificity of 75 % and 81 %, respectively, but on AFI all neoplasias were purple (sensitivity 100 %) [81].

A comparison of the effectiveness of AFI vs. CE in IBD has yet to be published.

4.6.4 Fluorescence Endoscopy

Sensitizers are molecules that accumulate selectively in malignant and premalignant tissue and fluoresce under blue light excitation; thus, they are highly useful in targeted biopsies. 5-Aminolevulinic acid (5-ALA), a prodrug in heme biosynthesis, is converted intracellularly into the sensitizing agent protoporphyrin IX. Due to the low ferrochelatase activity of tumor cells, protoporphyrin IX accumulates selectively in neoplastic tissue [82] and thus allows the detection of dysplasia by typical red fluorescence after illumination with blue light. Promising results for fluorescence endoscopy of bronchial [83] and bladder [84] tumors after 5-ALA sensitization have been reported.

Messmann et al. [69] assessed the efficacy of fluorescence endoscopy after 5-ALA sensitization for detecting dysplasia in UC. Optically guided biopsies were performed with fluorescence endoscopy after oral (20 mg/kg) or local (either with an enema or by spraying the mucosa via a catheter) sensitization with 5-ALA. In their study, the sensitivity of fluorescence endoscopy for dysplastic lesions was 87–100 % after local sensitization. The authors concluded that fluorescence endoscopy after 5-ALA sensitization can be used to visualize dysplastic lesions [69].

4.6.5 Confocal Laser Endomicroscopy

Confocal laser endomicroscopy is a promising method that allows for instant in vivo histology during ongoing endoscopy, but limited data regarding its use are available [56].

Two probe devices have been approved: one is integrated into the distal tip of a high-resolution endoscope (iCLE; Pentax, Tokyo, Japan), and the other is a standalone probe that is introduced through the instrument channel of standard endoscopes (pCLE; Cellvizio, Mauna Kea Technologies, Paris, France) [59, 71]. The functional principle is based on the fluorescence of mucosal tissue when exposed to blue laser light at an excitation wavelength of 488 nm, with light emission detected at 505 nm [59]. The resulting images provide an approximately 1,000-fold magnification of the tissue in vivo [71]. For confocal imaging, a fluorescence agent is administered either systemically (fluorescein sodium) or topically (e.g., acriflavine or cresyl violet) with fluorescein sodium [85]. Kiesslich et al. [61] conducted a randomized controlled trial to assess the effectiveness of combined CE and endomicroscopy in the diagnosis of intraepithelial neoplasias. They randomized

161 patients with UC in remission either to conventional colonoscopy or to chromoscopy with endomicroscopy to detect dysplasia or CRC. In the conventional colonoscopy group ($n = 73$), random and targeted biopsy examinations were performed. In the endomicroscopy group ($n = 80$), circumscribed mucosal lesions were identified by chromoscopy and evaluated for targeted biopsy by endomicroscopy. By using chromoscopy with endomicroscopy, the number of neoplasias that could be detected increased by 4.75-fold ($P = 0.005$) compared with conventional colonoscopy, but 50 % fewer biopsy specimens ($P = 0.008$) were required. The presence of neoplastic changes was predicted with high accuracy (94.7 % sensitivity, 98.3 % specificity, and 97.8 % accuracy). The authors concluded that endomicroscopy based on in vivo histology can determine whether UC lesions identified by chromoscopy should undergo biopsy examination, thereby increasing the diagnostic yield and reducing the need for biopsy examinations [61].

Hurlstone et al. [86] performed a prospective randomized controlled study to compare the diagnostic yield of intraepithelial neoplasia and cancer in patients undergoing UC screening using chromoscopy-assisted endomicroscopy vs. pancolonic chromoscopy-assisted colonoscopy. Endomicroscopy-targeted biopsies increased the diagnostic yield of intraepithelial neoplasia compared to chromoscopy-guided biopsies alone by 2.5-fold [86]. In addition to the improved detection, chromoscopy-guided endomicroscopy offers considerable cost savings.

4.7 Effectiveness of Cancer Surveillance in Reducing CRC-Related Death in UC

As noted above (Sect. 4.5), UC-associated CRC sometimes occurs as flat or diffuse infiltrative macroscopic lesions that are difficult to see endoscopically. Dysplasia is considered to be a precancerous lesion, and its presence is associated with a high likelihood of a complicating cancer, either nearby or in another region. Therefore, in surveillance colonoscopy, dysplasia is considered as a useful marker for detecting UC-associated CRC [87–89]. Accordingly, any screening or surveillance program must include a search for dysplastic alterations, to enable their treatment and to prevent the development of invasive cancer. While prophylactic proctocolectomy eliminates the risk of CRC, this strategy is not acceptable to most patients or physicians [90]. However, no randomized controlled trials have been performed to verify that surveillance colonoscopy is effective. A previous Japanese study reported that close surveillance results in the detection of 48 % of the cancers, 61 % of which are early cancers [91].

In 2006, the Cochrane Database of Systematic Review assessed the effectiveness of cancer surveillance programs in reducing the death rate from CRC in patients with UC and colonic CD [92, 93]. Three case-control studies were examined. In a population-based, nested case-control study of 142 patients with UC (derived from a study population of 4,664 patients with UC) reported by Karlen et al. [94], two of

the 40 patients with UC and CRC who died and 18 of the 102 matched controls with UC and CRC who were alive at the time of the death of the patient had undergone at least one surveillance colonoscopy (RR = 0.28; 95 % CI, 0.07–1.31) [94]. One of the 40 patients who died had undergone surveillance colonoscopies on two or more occasions compared with 12 out of the 102 controls (RR = 0.22; 95 % CI, 0.03–1.74).

In a study published in 1993, Choi et al. [95] examined 41 patients who developed CRC. Fifteen of the 19 patients had Dukes' A or B carcinoma in the surveillance group compared with nine out of 22 patients in the non-surveillance group ($P = 0.039$). The 5-year survival rate was 77.2 % in the surveillance group and 36.3 % in the non-surveillance group ($P = 0.026$). Four of the 19 patients in the surveillance group died from CRC compared to 11 of the 22 patients in the non-surveillance group (RR = 0.42; 95 % CI, 0.16–1.11).

In the 1991 study of Lashner et al. [96], four of 91 patients who underwent surveillance died of CRC, compared with two of 95 patients who did not undergo surveillance (RR = 2.09; 95 % CI, 0.39–11.12). Colectomy was less common in the surveillance group (33 vs. 51; $P < 0.05$) and was performed, on average, 4 years later (after 10 years of disease) than in the non-surveillance group, although improvement was not related to the anticipated benefits of improved cancer-related survival.

The review concluded that, for patients with UC undergoing surveillance, cancer tend to be detected at an earlier stage and patients therefore have a better prognosis, even if lead-time bias may contribute to the apparent benefit of surveillance. Indirect evidence supports the effectiveness of surveillance in reducing the risk of death from IBD-associated CRC and suggests that surveillance is cost-effective, although there is no clear evidence that it prolongs survival in patients with extensive colitis [92, 93].

4.8 Initial Screening and Surveillance Programs in Patients with CD

The effectiveness of surveillance in Crohn's colitis has been assessed in only a few studies. Friedman et al. [97] analyzed 1,424 examinations of 259 patients. On screening examination, definite dysplasia or cancer was found in 18 patients (7 %) (low-grade dysplasia, 13; high-grade dysplasia, 2; cancer, 3). On surveillance examinations, an additional 30 patients (14 %) had a first finding of definite dysplasia or cancer (low-grade dysplasia, 22; high-grade dysplasia, 4; cancer, 4). However, the appropriate screening and surveillance programs for long-standing CD have not been established yet.

The Crohn's & Colitis Foundation of America consensus conference recommendations for surveillance colonoscopy in patients with CD of the colon are as follows [98]:

1. Patients with major colonic involvement (at least one-third of the colon involved) who have harbored disease for 8–10 years from onset of symptoms should undergo a screening colonoscopy.
2. If no dysplasia or cancer is detected, a surveillance examination protocol should be started within 2 years.
3. After a negative surveillance colonoscopy, subsequent surveillance should be performed every 1–2 years. With two negative examinations, the next surveillance examination may be performed in 1–3 years until Crohn's colitis has been present for 20 years. At that time, surveillance should be performed every 1–2 years.

The BSG guideline recommends that all patients, not only those with UC but also those with Crohn's colitis, should undergo a screening colonoscopy approximately 10 years after the onset of colitis symptoms to assess disease extent and other endoscopic risk factors [45].

The AGA Institute Technical Review for surveillance colonoscopy in IBD recommends screening and surveillance not only for patients with long-standing UC but also for those with Crohn's colitis who have a disease involving at least one-third of the length of the colon [46].

There are currently no screening and surveillance programs aimed at detecting small bowel cancer. Further investigation, including a detailed meta-analysis of individual patients, is required to fully elucidate the risk of CRC and small bowel cancer in patients with CD [11].

4.9 Surveillance for Cancer Associated in CD Patients with Perianal Fistulas

Thomas et al. [99] analyzed 61 cases of cancer arising from perineal fistulas in patients with CD and found that a malignancy was suspected and proven in only 20 % of the patients on initial examination. Symptoms in patients with cancer arising from perineal fistulas in CD are usually nonspecific. A high level of attention must be paid to patients with long-standing perianal disease who have a change in symptoms. Clinical inspection or endoscopic examination is often insufficient because of anal pain and stricture, which may limit proper examination without anesthesia and in some cases even with anesthesia. Imaging studies including computed tomography, magnetic resonance imaging, or 18F-fluorodeoxyglucose positron emission tomography have a low sensitivity for detecting cancer in these patients [100,101]. Therefore, scheduled examinations and biopsy under anesthesia are necessary to diagnose anorectal cancer arising from a long-standing perianal fistula in CD [101].

A multicenter pilot study to determine an appropriate surveillance program for cancer arising from perineal fistulas in patients with CD is currently underway in

Japan, with Health and Labour Sciences Research Grants from the Ministry of Health, Labour and Welfare.

4.10 Factors Influencing the Success of Surveillance Colonoscopy

4.10.1 Precise Endoscopic Diagnosis

The endoscopic detection of dysplasia can be challenging and depends on the skills of the endoscopist. In a retrospective study, even after excluding polypoid cancers and apparent tubular adenomas, only approximately two-thirds of dysplastic lesions in patients with UC were visible [65]. Not all dysplastic lesions in IBD colons are visible with WLE, CE, and the newer high-definition colonoscopes. Surveillance colonoscopy should be performed on patients during clinical remission, to avoid confusing inflammatory changes with dysplasia [12]. Anatomic factors such as strictures and inflammatory pseudopolyps may interfere with the ability to detect or sample colonic dysplasia or cancer [46]. High-quality bowel cleansing and inactive mucosal disease are important to the success of a detailed mucosal examination [59].

4.10.2 Precise Histopathologic Diagnosis

Therapeutic recommendations for the management of dysplasia in UC are based on a macroscopic pattern (flat or elevated) and the microscopic characteristics of the lesion (indefinite, low-grade, or high-grade). Dysplasia almost certainly evolves along a progressive (continuous) scale rather than in discrete steps. Therefore, the interpretation of the grade of dysplasia varies even among experienced gastrointestinal pathologists [44, 102, 103]. Specimens with high-grade dysplasia are often considered negative, whereas those with indefinite and low-grade dysplasia are evaluated inconsistently. These limitations in the assessment of dysplasia have led to the recommendation that histologic findings should be confirmed by a second expert gastrointestinal pathologist [44].

4.10.3 Adequacy of Mucosal Sampling

The success of surveillance also depends on the adequacy of mucosal sampling. Detection of dysplasia may be affected by the number of biopsy specimens obtained

at colonoscopy. Guidelines for surveillance colonoscopy in the United States and Europe recommend the use of step biopsy [46].

4.10.4 Frequency of Surveillance

The frequency of surveillance may influence the success of a surveillance program. The precise interval for performing surveillance colonoscopies has not been rigorously studied [46]. Indeed, dysplasia or cancer has been detected within 2 years of a negative surveillance colonoscopy [104, 105].

4.10.5 Patient Acceptance

Patient acceptance is important to the success of surveillance [104, 106]. In a case-control study by Eaden et al. of 102 cases of CRC in UC, more than two yearly visits to the hospital physician were associated with a decreased risk of developing CRC [107].

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Chapter 5
Molecular Alterations in Inflammatory Colonic Carcinogenesis and Markers for Detecting Colitis-Associated Cancer

Yuji Toiyama, Toshimitsu Araki, Koji Tanaka, Yasuhiko Mohri, and Masato Kusunoki

Abstract The incidence of colorectal neoplasia is higher among patients with long-standing and extensive ulcerative colitis (UC) and Crohn's disease (CD), such as that for these patients surveillance colonoscopy is widely recommended. However, colitis-associated cancer (CAC) is often difficult to detect endoscopically and histologically because of modifications of the mucosal structure by inflammation. Repeated flare-ups of inflammation are believed to promote oncogenic insults to the colonic epithelium. Chronic inflammation and thus the increased turnover of epithelial cells contribute to the development of low-grade and high-grade dysplasia and therefore, over time, CAC. This is a different sequence of tumorigenic events that occurs in the development of sporadic CRC. Although the genetic and epigenetic features that lead to sporadic CRC (chromosomal instability, microsatellite instability, DNA methylation, and microRNAs) also occur in CAC, in the inflamed colonic mucosa, unlike the normal mucosa, these molecular alterations take place before there is any histopathologic evidence of dysplasia and cancer. Recently, several molecular alterations of the nonneoplastic epithelium have been identified in UC patients with neoplasia. These alterations may be promising as markers for identifying patients at high risk of developing CAC.

Keywords Inflammatory bowel disease • Colitis-associated cancer • Carcinogenesis • Molecular alteration • Diagnosis

5.1 Introduction

Patients with long-standing inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), are at a higher risk than the general population of developing colorectal cancer (CRC). This risk increases with a longer

Y. Toiyama (✉) • T. Araki • K. Tanaka • Y. Mohri • M. Kusunoki
Department of Gastrointestinal and Pediatric Surgery, Division of Reparative Medicine, Institute of Life Sciences, Graduate School of Medicine, Mie University, 2-174 Edobashi, Tsu, Mie 514-8507, Japan
e-mail: ytoi0725@clin.medic.mie-u.ac.jp

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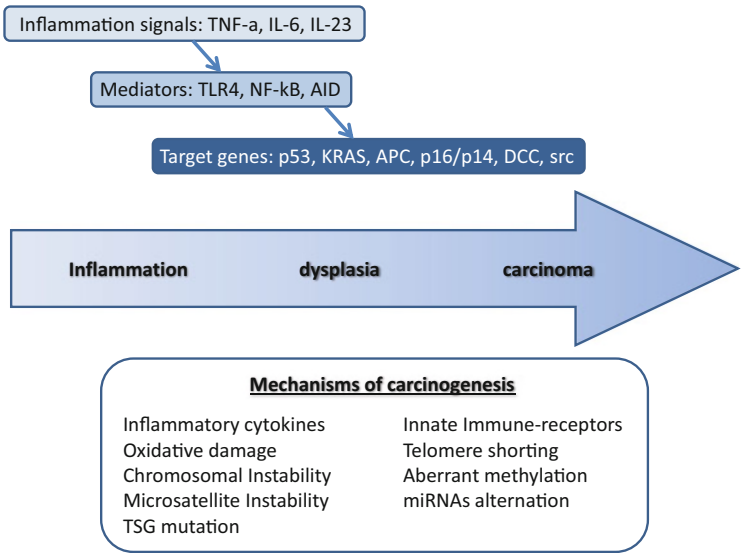

Fig. 5.1 Molecular pathogenesis of colorectal dysplasia and cancer in inflammatory bowel disease. Summary of the molecular signals, mediators, gene targets, and mechanisms implicated in the progression from mucosal inflammation to dysplasia to cancer. Abbreviations: *AID* activation-induced cytidine deaminase, *IL* interleukin, *TLR* Toll-like receptor, *TNF* tumor necrosis factor, *TSG* tumor suppressor gene

duration of colitis, the greater extent of inflammation, a family history of CRC, the severity of bowel inflammation, and a coexistent primary sclerosing cholangitis. The cornerstone for comprehending the development of colitis-associated cancer (CAC) in IBD and hence its early detection is based on an understanding of the molecular pathways of IBD itself. At a molecular level, the pathogenesis of CAC is related to the inflammatory changes, which involve multiple interrelated pathways including: (1) mucosal inflammatory mediators, such as cyclooxygenase-2 (Cox-2), interleukin (IL)-6, IL-10, tumor necrosis factor (TNF)-α, nuclear factor-kB, and chemokines; (2) oxidant stress; (3) changes in the expression of immune receptors on epithelial cells, including Toll-like receptors and Nod1; and (iv) genetic alterations, such as chromosomal and microsatellite instability, hypermethylation, and microRNAs (Fig. 5.1). The aim of this review is to provide an evidence-based approach to the role of chronic inflammatory mechanisms and their molecular basis in the development of CAC. An understanding of the molecular basis of CRC is an important step in the identification of new biomarkers that can help in the early detection of malignancy.

5.2 Inflammation

During inflammation, the destiny of an epithelial cell is determined by the balance between pro- and anti-tumorigenic immune responses. Inflammation participates in the three main stages of carcinogenesis: tumor initiation, tumor promotion, and tumor progression. Tumor initiation defines the process by which a normal cell becomes premalignant. The inflammatory condition, in which the levels of cytokines, chemokines, and reactive oxygen and nitrogen species are increased, induces DNA mutations, epigenetic alterations, and genomic instability, all of which contribute to tumor initiation [1, 2]. Tumor promotion leads to the proliferation of genetically altered cells, which is enhanced by inflammation via the acceleration of anti-apoptosis, proliferation, and angiogenesis [1, 2]. Finally, genetic changes influenced by inflammation advance tumor spread from the primary site to multiple distant sites (metastasis) [1, 2]. Thus, inflammation and malignant tumor formation are closely connected at all stage of tumorigenesis.

Much of the current evidence regarding the inflammatory mediators of CAC comes from murine models, which have provided insights into the carcinogenic process [3]. For example, IL-10-deficient mice develop spontaneous colitis and colonic neoplasms similar to those that occur in patients with CD [4]. Mice can also be treated with the mucosal irritant dextran sulfate sodium (DSS), with or without the mutagenic agent azoxymethane (AOM), which induces damage similar to that seen in UC patients, following a dose-repeated oral administration, colitis, and colonic neoplasm [5–7]. Through animal models, it is now known that inflammatory cytokines, chemokines, cell-surface receptors, and microbiota in the gut play crucial roles in colitis-associated carcinogenesis.

Cytokines exhibit both pro-inflammatory and anti-inflammatory effects, the balance of which plays an important role in CAC [3]. TNF-α, a pro-inflammatory cytokine, is an important mediator of chronic inflammatory disease, including IBD. TNF-α levels are consistently upregulated in the blood and colonic mucosa of patients with IBD [8]. In carcinogenesis, TNF-α acts as a tumor initiator by stimulating the production of reactive oxygen species, which cause oxidative stress and thus DNA damage and mutations and, in turn, tumor promotion, by altering cell proliferation and cell death [9–11]. Consistent with the critical role of TNF-α in chronic inflammation, anti-TNF-α monoclonal antibody biologics, such as infliximab, adalimumab, and certolizumab pegol, have proven to be effective in the treatment of IBD [10]. Furthermore, in an in vivo study using a mouse model of colitis, a monoclonal anti-TNF-α antibody reduced the development of tumors [2]. These results confirm the critical role of TNF-α in chronic inflammation and CAC. The pro-inflammatory cytokine IL-6 mediates a wide variety of inflammation-associated diseases. IL-6 levels are increased in IBD, CRC, and CAC and contribute to CAC development by promoting the survival of neoplastic epithelial cells in the colon [12–15]. Thus, the blockage of IL-6 signaling transduction could be a useful therapeutic system for the treatment of CAC [16]. IL-6 is also involved in promoting the growth and tumorigenesis of colon cancer cells by

altering the epigenome, such as silencing of DNA methyltransferase 1 (DNMT1)-mediated tumor suppressor genes [17]. Therefore, IL-6 appears to play a critical role in inflammation-associated carcinogenesis, although the molecular mechanisms are still being elucidated. Another important regulator of the immune response is the anti-inflammatory cytokine IL-10; its function is to block nuclear factor-kappaB (NF-kB) activity and to regulate the Jak-Stat signaling pathway [18, 19]. In addition, IL-10 downregulates TNF-α, vascular endothelial growth factor, and IL-6 production, which may account for its inhibitory effect on the tumor stroma [20]. IL-10 null mice develop spontaneous, generalized colitis and CAC in the presence of enteric bacteria. [21], whereas the administration of IL-10 improves the colitis and reduces tumor development by 50 %, even after colitis establishment [22]. Therefore, an incorrect balance of both pro- and anti-inflammatory cytokines is critical to both inflammation and inflammation-associated carcinogenesis.

Intraluminal bacterial endotoxins, TNF-α, and other pro-inflammatory cytokines act through extracellular receptors such as Toll-like receptors (TLRs) to initiate the phosphorylation cascades that transmit signals to key transcription factors such as NF-kB [23, 24]. TLR-4, which specifically responds to bacterial lipopolysaccharide ligand and is expressed at low levels in normal intestinal mucosa, is upregulated in the mucosa of patients with IBD, in the ileal mucosa of UC patients with pouchitis, in UC-associated CRC, and in colon tumors that develop in the AOM/DSS mouse model [25–27]. By contrast, TLR-4-deficient mice develop fewer and smaller tumors and produce less Cox-2 and prostaglandin E2, both of which mediate colorectal tumorigenesis. Conversely, mice deficient in the cytoplasmic immune receptor Nod1 and treated with AOM/DSS develop more severe colitis and larger tumors in the colonic mucosa compared to controls [28]. Taken together, these observations show that interactions between commensal bacterial components, elements of the innate immune response, and inflammation-induced tumorigenesis [29] are important for the initiation and maintenance of both chronic inflammation and tumor progression, through processes that involve NF-kB-regulated cytokines, chemokines, angiogenic factors, anti-apoptotic factors, and matrix proteases.

The mechanisms by which inflammatory cytokines promote the epithelial DNA mutations necessary for the initiation of neoplasia remain largely undefined. However, a potential mechanism has recently emerged from the study of activation-induced cytidine deaminase (AID), an enzyme that under physiologic conditions regulates class switching and somatic hypermutation in the immunoglobulin genes of activated B cells. AID induction by pro-inflammatory cytokines in human colon cancer cell lines was shown to lead to the accumulation of mutations in the tumor suppressor gene p53 [30]. AID is overexpressed in both neoplastic and nonneoplastic colonic epithelium from patients with IBD, as well as in some sporadic colon cancers. Therefore, this mechanism may account for the production of other potentially carcinogenic mutations in colonic epithelial cells in response to the overexpression of pro-inflammatory cytokines.

5.3 Oxidative Stress

Inflammation gives rise to colonic carcinogenesis by generating oxidative stress. IBD has been viewed as an oxyradical overload disease, in which long-standing inflammation increases the risk of malignant tumors [31]. Oxidative stress causes cellular damage that contributes to the pathogenesis of the colitis itself and to colon carcinogenesis. The initiation of tumor formation in chronic inflammatory tissue might be induced by reactive oxygen and nitrogen species (RONS), which are released by cells of the innate immune system. The inflamed colonic mucosa of patients with active IBD-associated colitis is characterized by the increased expression of nitric oxide synthase (NOS) and RONS [32–34]. Additionally, McKenzie et al. demonstrated the oxidation of thiols in the active site of glyceraldehyde-3-phosphate dehydrogenase, with subsequent inhibition of enzyme activity, in colonic epithelial cells from the inflamed mucosa of patients with IBD but not from paired samples of non-inflamed mucosa [35]. Furthermore, measurements of 8-hydroxydeoxyguanosine in mucosal biopsies from patients with UC showed that oxidative DNA damage progressively accumulates with the increasing duration of UC, reaching maximal levels in dysplastic lesions. This observation has implications for mutagenic and carcinogenic progression.

There is also evidence regarding the mechanisms of colorectal carcinogenesis induced by oxidative stress. Free radicals affect many metabolic processes, including those that regulate DNA, RNA, proteins, and lipids [31, 36]. When free radicals alter the genes or proteins that maintain homeostasis in intestinal epithelial cells, for example, p53, a dysplastic lesion forms and ultimately CAC. Hussain and coworkers [37] compared mutations of p53 in biopsy samples collected from the inflamed colonic mucosa of UC patients and from the normal mucosa of individuals without UC. The majority of the UC samples had a high frequency of p53 mutations compared with the control. In addition, these mutations were found only in inflamed not in non-inflamed mucosa. Another group showed that hydrogen peroxide inactivated the mismatch repair (MMR) system in colorectal cancer cell lines, apparently by damaging the protein complexes responsible for DNA repair [38] and causing microsatellite instability (MSI). In fact, MSI has been detected in the chronic inflammatory mucosa of UC patients, even in those with short disease duration, before the risk of dysplasia or CAC increases [39]. By contrast, MSI was not found in the colonic mucosa of healthy controls or that of patients with benign colitis or that of patients with CD [39, 40]. Thus, only a specific type of UC-induced colitis appears to cause MSI.

Several animal models have demonstrated that RONS participate in colitis-induced carcinogenesis. The application of peroxynitrite to the rat rectum was shown to cause colonic inflammation [41]. Scavengers of oxygen radicals (such as superoxide dismutase), catalase, and NOS inhibitors attenuate inflammation of the colon in animal models of chemically induced colonic injury [42]. Likewise, mice with inducible knockout of NOS develop attenuated colitis in response to injury [43], and APCmin/+ mice, carrying a mutation in the adenomatous polyposis

coli gene that causes multiple intestinal adenomas, developed fewer adenomas when they were crossed with mice carrying an inducible knockout of NOS or given an inducible NOS inhibitor. Although APCmin/+ mice are not considered to be models of colon cancers that arise from colitis, these data support the concept that oxidative stress promotes colon carcinogenesis. The fact that mice deficient in glutathione peroxidase enzymes develop inflammation and cancer of the small and large intestines also supports a model in which antioxidant pathways prevent the transition of inflammation to neoplasia.

5.4 Genetic Instability

Genetic instability can be divided into two clinically distinct forms, both of which have been extensively studied in CRC: chromosomal instability (CIN) and MSI [44]. CIN and MSI are detected with the same frequency in CAC (85 % CIN, 15 % MSI) as in sporadic CRC [45]. CIN is manifested by genomic alterations that affect large DNA segments, resulting in aneuploidy, translocations, deletions, gene copy amplifications, and telomere shortening. It is typically associated with the progressive accumulation of mutations in onco-suppressor genes (APC, p53) and oncogenes (KRAS). MSI can be preceded by the alternation/inactivation of DNA repair mechanisms, including nucleotide excision repair, base excision repair, and MMR [46]. Furthermore, besides the many genetic contributions to CIN and MSI, epigenetic elements can affect tumor initiation, proliferation, and metastasis. In particular, the hypermethylation of onco-suppressor DNA promoter regions and microRNAs are major epigenetic mechanisms of gene silencing in colorectal carcinogenesis [47].

5.4.1 Chromosomal Instability

The extent and types of CIN associated with IBD-related dysplasia and CAC have been evaluated by comparative genomic hybridization, fluorescent in situ hybridization (FISH), flow cytometry, and DNA fingerprinting. CIN in IBD, in addition to its similar frequency to CIN in sporadic carcinogenesis, also affects many of the same loci and results in similar mean numbers of chromosomal alterations per case [45, 48]. An important distinction, however, is that CIN in UC is distributed broadly, involving even mucosa that is negative for and remote from dysplasia, whereas in sporadic CRC it is restricted to tumor tissues [45, 49, 50]. Chromosomal alterations therefore appear to occur early in the course of IBD-related neoplastic progression and prior to the histologic features of dysplasia. CIN is typically absent in patients with UC who do not also harbor dysplasia or CAC. Thus, the presence or absence of CIN in nonneoplastic mucosa has been advanced as a marker enabling patients to be stratified into distinct categories of progressors and non-progressors,

respectively [45, 49, 51–53]. Progressors have an earlier onset and longer duration of disease [54]. Recently, the FISH-based detection of combined alterations in four key chromosomes in nonneoplastic mucosa was reported to be 100 % sensitive and 92 % specific in distinguishing progressors from non-progressors, suggesting the application of this method to improve surveillance [55]. One proposed mechanism by which chronic inflammation could lead to CIN involves accelerated telomere shortening. The telomeres of colonic epithelial cells from patients with UC are shorter than those of the colonic epithelial cells of healthy controls. This difference is attributable to the faster cell turnover, increased replication, and increased oxidative damage that result from repeated cycles of injury and regeneration [56, 57]. Telomere shortening in turn correlates with CIN, as reflected by the higher rates of chromosomal arm and centromere loss and the higher frequency of anaphase bridges in the colonic epithelium of patients with UC who have dysplasia or CAC but not in that of controls [53]. Telomere shortening beyond a critical point is associated with aging as well as growth arrest, through replicative senescence when DNA damage checkpoints are intact, but through chromosomal damage, such as breaks and end-to-end fusions, when these checkpoints are defective [58, 59]. Thus, telomere shortening could facilitate CIN, provided that DNA damage checkpoints are somehow also inactivated through mutations of checkpoint genes such as p53. The rates of telomere shortening in the colonic epithelial cells of patients with UC are double those seen in healthy controls and occur mostly during the first 8 years of disease, the time frame when the risk of CRC begins to become clinically significant [57].

Aneuploidy occurs in approximately 33 % of patients with long-standing UC, in 20–50 % of dysplastic lesions, and in 50–90 % of cancers [60]. Regions of aneuploidy in the large bowel of UC patients are frequently those exhibiting dysplasia. Since aneuploidy precedes the appearance of histologic changes, it may be a useful marker of developing neoplastic lesions in UC patients. Despite the utility of flow cytometry in assessing aneuploidy in patients with IBD, it is not widely available and thus cannot be universally applied in the follow-up of patients with long-standing UC.

The timing and frequency of DNA mutation differs in CAC vs. sporadic CRC (Fig. 5.2). Loss of APC function, an early event in the progression of sporadic CRC, is less frequent and usually occurs at the late stage of CAC development [61–63]. APC mutations are rarely, if ever, detected in cells of the colitic mucosa that are negative or indefinite for dysplasia, and <14 % of tissues with low-grade dysplasia or CAC have mutations in APC [61, 62, 64]. Likewise, allelic deletion of APC occurs in <33 % of CAC cases [64]. Loss of p53 function is an important step in CAC progression, and allelic deletion of p53 is observed in 50–85 % of CACs [65, 66]. Loss of heterozygosity (LOH) at p53, which correlates with malignant progression, was detected in 6 % of biopsy samples without dysplasia, 9 % with indefinite dysplasia, 33 % with low-grade dysplasia, 63 % with high-grade dysplasia, and 85 % with CAC [65]. Mutations in p53 are found in the colon tissue of patients with colitis and often in mucosa that is nonneoplastic or only indefinite for dysplasia [65–67]. In carefully mapped colectomy specimens, p53 mutations

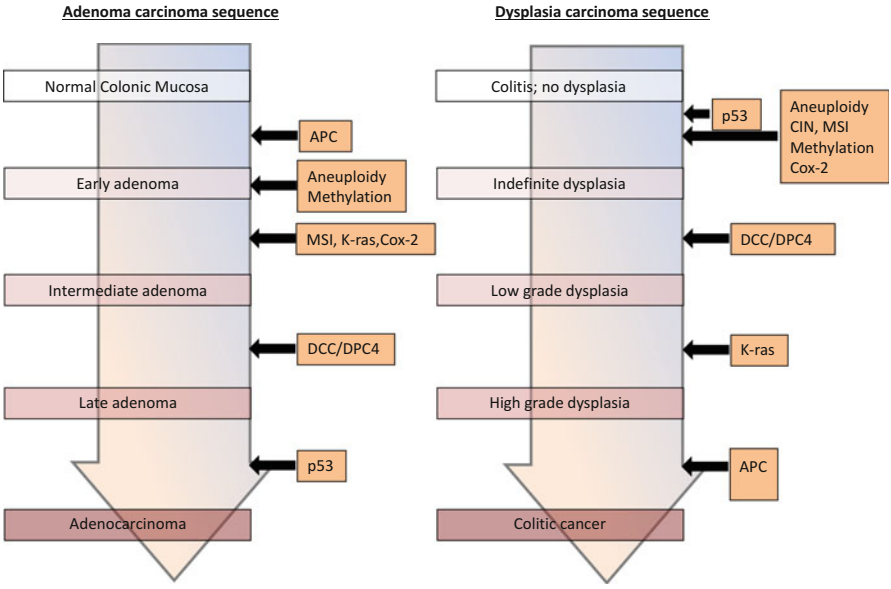

Fig. 5.2 Comparison of the molecular alterations in sporadic colon cancer (*left*) and colitis-associated colorectal cancer (*right*). There are similarities between the two pathways, including the development of chromosomal instability, microsatellite instability, DNA methylation, activation of the KRAS oncogene and of cyclo-oxygenase (Cox)-2, and mutation and the eventual loss of heterozygosity of p53, the adenomatous polyposis coli (APC) gene, and the deleted in colorectal carcinoma (DCC) genes DCC/DPC4. However, the frequency and sequence of these events differ between the pathways

were shown to occur early in tumorigenesis, before aneuploidy [66, 67]. In fact, mutations were found in inflamed mucosa from >50 % of UC patients who did not have CAC, indicating that chronic inflammation caused these mutations [37]. Mutations of the KRAS proto-oncogene, present in 40–60 % of sporadic CRCs, are probably an early event in these cancers [68], whereas they occur at a lower but significant frequency (24 %) in CAC [69]. Thus, KRAS mutations probably play a significant role in the later stage of CAC. The tumor suppressor gene Rb is often mutated or lost in epithelial tumors. In UC-associated carcinogenesis, Rb LOH is present in 20 % of dysplasia and 30 % of CAC specimens [70]. Finally, losses at chromosome 18q are relatively rare events in the sequence of dysplasia → carcinoma in UC. LOH of 18q, the site of the deleted in colorectal carcinoma gene, was observed in 12 % of CACs and 33 % of dysplasias but not in nonneoplastic lesions or inflamed mucosa [71].

5.4.2 Microsatellite Instability

Microsatellites are short repetitive sequences (one to five nucleotides) of DNA that are randomly distributed throughout the whole genome. MSI involves the loss of function of several genes (hMSH2, hMLH1, hPMS1, hPMS2, hMSH6, and hMLH3) that repair DNA base-pair mismatches. DNA MMR deficiency results in a strong mutator phenotype and MSI [72]. The stability of these sequences is a good measure of the general integrity of the genome. MSI reflects a gain or loss of repeat units in a germline microsatellite allele, consistent with the clonal expansion that is typical of cancer. UC-associated carcinogenesis can also be associated with MSI. A high rate of MSI in long-standing UC is probably related to the genomic instability produced by repeated inflammatory stimulation, and the influence of inflammation has been evaluated in estimates of MSI in UC [73]. Indeed, although the molecular mechanisms involved in the increased risk of CAC in UC are for the most part still unclear, many appear to be related to MSI [39]. The prevailing hypothesis is that the overproduction of free radicals overwhelms the ability of the cell to repair oxidative DNA damage prior to replication [39, 74]. Alternatively, prolonged and repeated oxidative insults may directly inactivate DNA MMR genes [38]. One study reported that half of UC mucosal samples with high MSI exhibit MLH1 hypermethylation [75]. However, in contrast to colon cancer in patients with hereditary non-polyposis, there is little evidence for MMR defects as a cause of MSI in UC [76, 77]. A recent report described the adaptive increased activity of 3-methyladenine DNA glycosylase (AAG) and apurinic endonuclease (APE1) in areas of the UC colon undergoing active inflammation [78]. This imbalanced increase appeared to be associated with the MSI characteristic of UC. These data were consistent with a possible novel mechanism by which the colonic cells of patients with chronic colonic inflammation acquire MSI. In UC patients, areas of the colonic epithelium with active inflammation exhibited increased AAG and APE1 enzyme activity; the largest increases and imbalances occurred in areas with inflammation as well as MSI. These observations suggest that the adaptive imbalanced increase in these enzymes has DNA-damaging effects and contributes to carcinogenesis in the chronically inflamed colon [78].

5.4.3 Aberrant DNA Methylation

Epigenetics, which includes histone modifications and DNA methylation, alters gene expression without changing the DNA sequence and can be transmitted to daughter cells. There is also significant cross talk between histone modifications and DNA methylation, both of which are highly dysregulated in many diseases, particularly in cancer [79, 80]. Epigenetic alterations are observed during inflammation and inflammation-associated carcinogenesis [81, 82]. DNA methylation involves the addition of a methyl group to the fifth carbon position in the pyrimidine

ring of cytosine located in the context of CpG dinucleotides. It is one of the most well-studied epigenetic processes and is maintained during replication by the enzyme DNMT1, whereas de novo DNA methylation is believed to be mediated by DNMT3A and DNMT3B. However, there is functional overlap between DNMT1, DNMT3A, and DNMT3B [83–85].

DNA methylation contributes to the development and progression of CAC. Methylation of CpG islands in several genes precedes dysplasia and can be detected throughout the mucosa of patients with UC [86]. Among CAC tissues from UC patients, hMLH1 hypermethylation was recognized in six of 13 specimens with high levels of MSI, one of six with low levels of MSI, and four of 27 without MSI [75], suggesting that methylation induces MSI. The attenuated expression of the cell cycle inhibitor gene p16INK4a is associated with sporadic CRC; p16INK4a is also frequently hypermethylated in neoplastic tissues from UC patients. Approximately 10 % of nonneoplastic lesions have hypermethylation of the p16 promoter; the rate increases with higher grades of dysplasia, reaching 100 % in CAC [87]. Additionally, p14ARF, an indirect regulator of p53, is encoded by the same gene as p16INK4a. Loss of expression of p14ARF by hypermethylation is frequently observed in the mucosa of UC patients. In one study, it was detected in 50 % of CAC, 33 % of dysplastic, and 60 % of nonneoplastic mucosal samples collected from UC patients compared with 3.7 % of normal colonic mucosa samples [88]. Another group investigated the methylation status of ten genes [p16, p14, runt-related transcript factor-3 (RUNX3), Cox-2, E-cadherin, methylated-in-tumor-1 (MINT1), MINT31, HPP1, estrogen receptor, and SLC5A8] in tissue samples from CAC and in nonneoplastic colonic mucosa from UC patients with and without neoplasia [89]. Methylation of the promoters of RUNX3, MINT1, and COX-2 was determined and suggests the use of these genes as biomarkers of the presence of CAC in patients with UC. Kuester et al. [90] demonstrated the hypermethylation of death-associated protein kinase (DAPK), a proapoptotic protein implicated in various apoptotic cascades, in UC-associated carcinogenesis in patients with long-standing disease. They also observed the overexpression of DAPK in inflamed colonic epithelium [90], indicative of a protective role for this protein. Thus, the inactivation of DAPK, mediated by promoter hypermethylation, might contribute to the accumulation of UC epithelial cells with genomic damage in response to inflammation and thus to the initiation of carcinogenesis and CAC.

The increasing evidence of inflammation-associated carcinogenesis includes a role for the key mediators of inflammation-induced DNA methylation: oxidative stress and increased levels of the pro-inflammatory cytokines, including IL-6, IL-β, TNF-α, and interferon-ɤ [17, 91–93]. The mechanisms by which these pro-inflammatory mediators alter DNA methylation during inflammation are not completely understood, but recent research has provided several insights. First, IL-6, the expression of which is increased during CAC, stabilizes DNMT1 protein levels in human colon cancer epithelial cells [17]. Second, interferon-ɤ was shown to increase nuclear 5'methylcytidine in human intestinal epithelial cell cultures by increasing DNMT3B mRNA levels [91]. Third, in an animal model of colitis, IL-1β expression was concordant with methylation induction, a phenomenon that is also

observed in *Helicobacter pylori* infection, in which increases in IL-1β and TNF-α levels occur in parallel with the temporal changes in methylation levels [93, 94]. Finally, in a colon cancer cell line exposed to oxidative stress, DNMT1 and repressive factors were recruited to GC-rich regions of the genome [92]. These findings suggest that factors produced during inflammation alter mediators of DNA methylation. Thus, the aberrant DNA methylation patterns, rather than being a response to chromosomal insult, may in themselves promote an inflammatory environment. This is supported by a mouse model of colitis, in which aberrant DNA methylation occurred in the absence of macroscopic tumors and gradually increased until tumors developed [94].

According to this scenario, 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. Whether the inflammation-induced increase in DNA methylation is targeted to specific regions of the genome or affects the genome as a whole remains to be determined.

5.4.4 MicroRNA Alterations

MicroRNAs (miRNAs) are 19–24 nucleotides long and serve as major regulators of gene expression, by targeting mRNAs post-transcriptionally [95]. Important roles for miRNAs have been confirmed in cellular differentiation, development, proliferation, and apoptosis. However, in cancer, these processes are deregulated, which implies that miRNAs are involved in carcinogenesis, perhaps at the tumor initiation and progression stages [96].

Indeed, increasing evidence suggests that miRNAs are involved in the carcinogenesis underlying CAC. Ludwig et al. [97] reported the upregulation of miR-21 in IBD-associated dysplastic lesions but not in tissues from patients with active IBD. The increase in miR-21 correlated inversely with the expression of PDCD4, a newly characterized tumor suppressor gene. Olaru et al. [98, 99] found that miR-224 and miR-31 expression increased successively at each stage of IBD progression, from non-inflamed to inflamed nonneoplastic, dysplastic, and finally cancerous mucosa. Both miR-224 and miR-31 levels could accurately discriminate normal or chronically inflamed IBD tissues from cancers. The authors also showed that miR-224 was involved in cell cycle regulation by targeting p21 and that miR-31, by targeting the negative repressor of hypoxia-inducible factor 1, regulated tumor angiogenesis, which would link both of these miRNAs to IBD-associated carcinogenesis.

In general, tumor-specific miRNA expression profiles are more informative and discriminatory than mRNA profiles. Furthermore, circulating miRNAs are highly resistant to RNase activity, unlike mRNA [100], which recommends their use as noninvasive biomarkers in the diagnosis of CAC. However, miRNA-based markers that confidently identify UC patients at increased risk of neoplasia have yet to be developed.

5.5 Molecular Markers to Identify the Risk of Neoplasia in UC Patients

CAC is a major cause of mortality in patients with UC [101, 102], such that diagnosis at an early or precancerous stage is crucial. A predisposition to colorectal neoplasia in UC is generally considered to depend on the diagnosis of UC at a young age and the presence of extensive colitis [103]. The prevalence of CAC in patients with UC is 8 % at 20 years after the initial UC diagnosis and increases to 18 % at 30 years [104]. Thus, surveillance colonoscopy with multiple random biopsies has been widely recommended for patients with long-standing and extensive UC [105]. However, because CAC is often difficult to detect endoscopically and its discrimination from inflammatory regenerative epithelium is histologically challenging, whether conventional surveillance colonoscopy is effective for the early detection of CAC remains a matter of contention. In addition, recent analysis demonstrated that the low yield and lack of clinical consequences from random biopsies in this high-risk population raise questions about the necessity and cost-effectiveness of routine random biopsy during UC surveillance [106]. Consequently, more accurate diagnostic modalities, such as chromoendoscopy and magnifying endoscopy, to identify potential sites of neoplasia in a nonneoplastic inflamed epithelium, together with analysis of p53 alterations, to distinguish neoplastic lesions from regenerative epithelium, have been evaluated [107, 108]. However, the labor-intensive nature and expense of these adjunctive modalities preclude their use in the surveillance of all UC patients with long-standing and extensive colitis. Rather, within this subgroup of patients, the ability to distinguish those who are at low vs. high risk of colorectal neoplasia would allow physicians to identify patients most likely to benefit from these more extensive screening methods.

5.5.1 Molecular Changes in the Nonneoplastic Mucosa in UC

The nonneoplastic mucosa of UC patients with CAC exhibits several molecular alterations (CIN, MSI, DNA aneuploidy, DNA methylation, telomere shortening, and gene expression), collectively referred to as a "field effect." These alterations in the nonneoplastic UC mucosa may be promising biomarkers that allow the identification of UC patients at high risk of CAC.

5.5.2 Utility of Age-Related Methylation in Identifying CAC

In most human cancers, aberrant hypermethylation of promoter CpG islands, leading to the inactivation of key tumor suppressor genes, is a frequent and early

step in tumorigenesis. In CRC, this epigenetic alteration is associated with two distinct subsets of genes: those that display a cancer-restricted methylation pattern (type C) and those that become methylated during aging (type A) [109]. Issa et al. [110] showed that the estrogen receptor (ER) of the normal colorectal mucosa becomes increasingly methylated with age and that hypermethylation of the ER gene is seen in most cases of sporadic CRC. Thus, age-related methylation may be an important contributor to the acquired predisposition to colorectal neoplasia and together with cancer-restricted methylation may be a feature of chronic inflammation-associated disease, including UC.

Issa et al. [86] were the first to demonstrate that the ER, MYOD, and CSPG2 genes and exon 1 of the p16 gene, all of which undergo age-related methylation in the colorectal mucosa, are intensively methylated in the high-grade dysplasia/CAC tissues of UC patients. Furthermore, they showed that these genes were also highly methylated in the nonneoplastic mucosa of these same UC patients. Accordingly, they proposed the use of age-related methylation as a molecular marker to identify UC patients at increased risk of developing dysplasia/CAC. This approach received support from another group that elegantly demonstrated high levels of ER gene methylation not only in regions of dysplasia/CAC but also in other regions widely scattered throughout the colorectum. The implication of the latter result is that analysis of a single biopsy sample (e.g., rectal biopsy) may suffice to identify higher-risk patients and that a large number of biopsy samples and total colonoscopy may not always be necessary [111, 112].

5.5.3 Methylation of the Putative Promoter Regions of miRNAs as a Marker of CAC in UC Patients

In an attempt to clarify whether age-related DNA methylation in nonneoplastic epithelium is an indicator of an increased risk for CAC, we selected miR-124, miR-137, and miR-34b/c as candidate genes, since their methylation is associated with increasing age and a field effect has been reported in the uninvolved colonic mucosa of patients with sporadic CRC [113–117]. We hypothesized that aberrant hypermethylation of the genes encoding these specific miRNAs in the normal, aging colorectal epithelium is an early event in CAC. Our systematic evaluation demonstrated the feasibility of using the methylation status of the miR-124, miR-137, and miR-34b/c genes as a promising biomarker in UC-associated neoplasia. When these biomarkers are used alone or in conjunction with the current guidelines for the diagnosis of UC-associated neoplasia, many of the current clinical challenges for managing these patients could be overcome. More importantly, the analysis of these biomarkers from a single rectal biopsy specimen has robust predictive potential in identifying UC patients at high risk for neoplasia elsewhere in the colorectum [118].

5.6 Conclusions and Perspectives

This chapter provided a review of the relationship between colonic inflammation and various tumor genetic events leading to CAC. The sequence of events ending in tumor formation is quite different from the events that give rise to the development of sporadic CRC. The early events in CAC involve DNA methylation, which regulates the expression of onco-suppressor genes, as well as mutation of p53, aneuploidy, and MSI. Tumor- and age-dependent methylation also occur in the nonneoplastic mucosa of UC patients with CAC, so-called field effects. A better understanding of the mechanisms for inflammation-induced carcinogenesis could identify IBD patients at high risk for CAC.

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Part III
Surgical Treatment

Chapter 6
Surgical Treatment for Ulcerative Colitis-Associated Cancer or Dysplasia

Toshimitsu Araki, Yuji Toiyama, Yoshiki Okita, Koji Tanaka, Yasuhiro Inoue, Keiichi Uchida, and Masato Kusunoki

Abstract Patients with long-standing ulcerative colitis (UC) have an increased risk of colorectal neoplasia (from dysplasia to advanced cancer) and are therefore candidates for several kinds of surgical treatments, ranging from an endoscopic resection to abdominoperineal resection and total proctocolectomy, depending on disease status. In addition to the extent of resection, patient age and sex, anal function, UC status, and type or location of the neoplasia must be taken into account in surgical decision-making. Although total proctocolectomy with ileal pouch-anal anastomosis is the gold standard for UC-associated colorectal cancer, the pros and cons of rectal mucosectomy are still debated. In addition, the postoperative administration of immunomodulators or biologics for UC is controversial. Data on the prognosis of surgically treated patients are still limited, and conclusions cannot yet be drawn. However, these patients should be closely followed for a relapse of inflammation and the recurrence of neoplasia in the residual lesion, especially in the anal transition zone. Recent, more aggressive approaches include chemoradiotherapy followed by ileal pouch-anal anastomosis or partial intersphincteric resection.

Keywords Ulcerative colitis • Surgery • Colorectal cancer • Dysplasia • Ileal pouch

6.1 Introduction

Previously, 25 % of the patients with ulcerative colitis (UC) underwent colectomy for medically refractory UC or UC-associated neoplasia. In recent years, however, elective colectomy rates in UC patients have decreased, as the efficacy of antitumor necrosis factor (TNF) antibodies has been confirmed and their use has increased significantly [1]. Nonetheless, patients with long-standing UC continue to be at

T. Araki (✉) • Y. Toiyama • Y. Okita • K. Tanaka • Y. Inoue • K. Uchida • M. Kusunoki
Department of Gastrointestinal and Pediatric Surgery, Division of Reparative Medicine, Institute of Life Sciences, Mie University Graduate School of Medicine, 2-174 Edobashi, Tsu, Mie 514-8507, Japan
e-mail: taraki@clin.medic.mie-u.ac.jp

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higher risk of colorectal cancer (CRC) than the general population and therefore often require surgery for UC-associated neoplasia. The early detection of cancers in UC patients means that the tumor can be treated at an earlier stage, which corresponds to a better prognosis [2].

Total proctocolectomy (PC) with ileal pouch-anal anastomosis (IPAA) is the procedure of choice for patients undergoing elective surgery for UC and is the standard procedure for those with UC-associated CRC. Clearly, there are fewer indications for IPAA in the treatment of UC-associated neoplasia than for medically refractory UC, given that in the treatment of CRC, the primary aim is to improve the oncologic prognosis, which takes precedence over the functional prognosis.

Recent technical progress in gastroenterological endoscopy has allowed the more accurate detection of dysplasia, which has led to renewed debate regarding the utility of endoscopic surveillance or resection for dysplastic lesions. The larger proportion of younger patients with UC-associated cancer than sporadic cancer in individuals with a normal mucosa has also led to a reconsideration of surgery for UC-associated cancer with respect to operative indication, extent of resection, and pros and cons of rectal mucosectomy. In this chapter, we discuss the various options for the surgical treatment of UC-associated cancer while taking into account the related controversies.

6.2 Surgical Indications for UC-Associated Neoplasia

Although the choice of treatment is influenced by the site and stage of the cancer, the detection of CRC by biopsy is an absolute indication for surgery in UC patients. UC-associated cancer is characterized by its broad range of macroscopic appearances, its tendency to spread diffusely and invasively, and its poorly marginated lesions; these features distinguish it from sporadic CRC [3]. Another important difference between sporadic and UC-related colonic neoplasia is that in the latter the entire colonic mucosa is at risk for neoplastic transformation, which can be multifocal [4]. The underlying mechanism is the inflammation → dysplasia → carcinoma sequence in patients with long-standing UC-related inflammation of the colon and rectum [5–7]. In addition, so-called field effects of multiple epigenetic alterations, including methylation, have been shown in both the neoplastic and non-dysplastic mucosa of UC patients [8–10]. Field effects have been attributed to the constant reepithelialization of the ulcerated and chronically inflamed colonic mucosa by abnormal cell clones that arise during healing and subsequently expand [11] and to changes in the local environment, such as oxidative stress and an altered bacterial flora, both of which can give rise to cellular mutations [12].

Dysplasia, the earliest histologic manifestation of neoplastic transformation, is defined as an unequivocal neoplastic change in the colonic epithelium without invasion into the lamina propria. Dysplasia is grouped into five main categories: low-grade dysplasia (LGD), high-grade dysplasia (HGD), dysplasia-associated

lesion or mass (DALM), adenoma-like mass (ALM), and adenoma-like DALM. The appearance of any of these is an early clinical alert to the development of carcinogenesis because the probability of a coexistent carcinoma is relatively high [13, 14]. However, some researchers maintain that the presence of dysplasia is associated with a low risk of unsuspected cancer at the time of colectomy [15]. Accordingly, the decision-making process for patients with UC who are considering intensive surveillance vs. surgical intervention after a diagnosis of dysplasia is a controversial one.

6.2.1 High-Grade Dysplasia

Over 30 % of the patients with HGD will develop cancer during subsequent surveillances; however, there are no reported instances in which HGD was subsequently downgraded to negative [7, 16, 17]. Among patients with HGD who underwent prophylactic colectomy immediately after diagnosis, about 40 % had cancer in the resected sample [7, 18–20]. Moreover, the HGD was detected at a colonic site distant from that of the synchronously detected cancer [19, 21]. Therefore, a diagnosis of HGD is an absolute indication for surgical resection [22–24].

6.2.2 Low-Grade Dysplasia

Whether patients with flat LGD should undergo surgery continues to be debated. Among patients with LGD with subsequent surveillance colonoscopy, 5–50 % subsequently had the diagnosis downgraded to indefinite or negative [17, 18, 20, 25]. However, in approximately 30 % of these patients, there was eventual progression to HGD, DALM, or cancer [7, 16–18, 20, 22, 25]. Cancer was eventually detected in approximately 10 % of the patients with LGD and subsequent surveillances [16, 18, 20, 22, 25–27]. Zisman et al. [28] showed that patients with three or more biopsies demonstrating LGD at a single colonoscopy had an increased risk of progression to advanced neoplasia [relative risk (RR) = 5.8; 95 % confidence interval (CI): 1.29–26.04].

Analyses of the outcomes of patients who underwent colonoscopic surveillance for 10 years following the detection of LGD did not show a statistically significant difference from the outcomes of control patients. This conclusion is supported by histopathologic reviews, which have demonstrated the unreliability of LGD diagnosis [29]. Thus, the current opinion is that a diagnosis of LGD does not justify prophylactic colectomy.

However, there are opposing views regarding whether only flat lesions should be followed up endoscopically, because dysplastic lesions, which eventually progress to invasive cancer, cannot be consistently and reliably detected through successive surveillances [30]. Bernstein et al. [22] analyzed ten prospective studies (1225

patients), in which the lesions of 16–29 % of the patients progressed from untreated LGD to DALM, HGD, or cancer. In their retrospective study, Kiran et al. [31] showed that the rate of the risk of cancer in postoperative pathologic findings was 3 % even if preoperative biopsies demonstrated LGD. In general, because advanced neoplasia can be found in association with dysplastic changes of any grade, patients with confirmed dysplasia of any grade should undergo colectomy [13, 22, 26, 31, 32].

According to the current American College of Gastroenterology guideline [33], surgery should be promptly considered in patients with flat LGD to prevent progression to a higher grade of neoplasia. In the Medical Position Statement of the American Gastroenterological Association [34, 35], multifocal LGD is a strong indication for colectomy. In addition, although controversial, there is evidence to suggest that patients with flat, unifocal, LGD should also be considered for colectomy [36, 37].

Primary sclerosing cholangitis (PSC) is typically associated with inflammatory bowel disease (IBD), particularly UC. PSC-IBD patients are at an increased risk of colorectal neoplasia [38]. In one-third of PSC-UC patients, LGD will progress to HGD/CRC. Venkatesh et al. [39] evaluated ten PSC-UC patients with LGD who underwent surveillance colonoscopy. In three (30 %) patients, LGD progressed to raised HGD over a mean follow-up of 13 ± 11 months, and HGD occurred more frequently within the first year of the initial detection of LGD (23.5 per 100 patient-years of follow-up). Therefore, PSC-UC patients with LGD should be closely and carefully followed.

6.2.3 Dysplasia-Associated Lesion or Mass

It was initially suggested that any dysplasia found in association with a DALM, in particular with a polypoid mass, indicates a high likelihood of the presence of synchronous or metachronous neoplasia [40]. Bernstein et al. [22] evaluated 40 patients with DALM from ten prospective studies (1225 patients); 17 (43 %) of the patients already had cancer at immediate colectomy. In another report of patients with HGD in DALM who were followed for over 5 years, none of the patients had carcinoma, either in surveillance biopsies or in resection specimens [41]. Thus, the latter authors concluded that the presence of HGD in DALMs does not warrant colectomy with continued close observation.

In a series of 348 patients from 1984 to 2007, Kiran et al. [31] demonstrated that those with a preoperatively detected DALM had a significantly higher risk of cancer than patients with flat dysplasia (25 % vs. 8 %; $P < 0.001$). They also found that the risk of cancer was not significantly higher in LGD with DALM than in flat LGD (7 % vs. 2 %; $P = 0.3$), but the risk of cancer or HGD was threefold higher (29 % vs. 9 %; $P = 0.015$).

Recent studies broadly separated the raised (endoscopically visible) dysplastic lesions in IBD into those resembling non-IBD-related sporadic adenomas

(adenoma-like) and those that do not resemble adenomas (non-adenoma-like) [42–44]. Biopsy specimens of non-adenoma-like DALMs may contain the surface of an invasive adenocarcinoma, which is regarded as endoscopically unresectable [40]. Thus, patients with UC and an endoscopically unresectable, non-adenoma-like DALM, regardless of the grade of dysplasia detected on biopsy analysis, should undergo colectomy, because of the high association of these lesions with metachronous or synchronous carcinoma [35, 45].

6.2.4 Stricture

A colonic stricture is regarded as a manifestation of chronic UC, although carcinoma may occur at the site of a stricture [46], and a fibrous stricture as an indication for surgery, owing to the possibility of malignant degeneration [47]. Gumaste et al. [14] investigated 1156 UC patients; in this group, 17 of the 70 strictures (24 %) proved to harbor a malignancy. In addition, they described three features that distinguish a malignant from a benign stricture: (1) appearance late in the course of UC (61 % probability of malignancy in strictures that develop after 20 years of disease vs. 0 % in those occurring before 10 years); (2) location proximal to the splenic flexure (86 % vs. 47 %, 10 %, and 0 % when the stricture is in the sigmoid colon, rectum, and splenic flexure and descending colon, respectively); and (3) symptomatic large bowel obstruction (100 % probability of malignancy vs. 14 % in the absence of obstruction or constipation) [14]. Lashner et al. [48] described 15 patients with UC-related strictures identified by air-contrast barium enema or on colonoscopy; within this group, 11 had dysplasia and two had cancer. Thus, a stricture should be considered as a strong risk factor for cancer, requiring intensive colonoscopic surveillance. If dysplasia is discovered or if the stricture cannot be adequately biopsied, then surgical treatment should be considered [48].

6.3 Surgical Procedure

The surgical procedure for neoplasia in patients with UC varies, ranging from colonoscopic resection to total PC. Although PC with permanent ileostomy and restorative PC with mucosectomy are the only surgical procedures that will reliably eliminate the cancer risk in UC, the risk of subsequent morbidity and impaired anal function is not small. The choice of surgical treatment is influenced by the site and stage of the neoplasia, the functional state of the rectum, the presence of multifocal lesions, the patient's age, and the duration of UC [49] (Fig. 6.1).

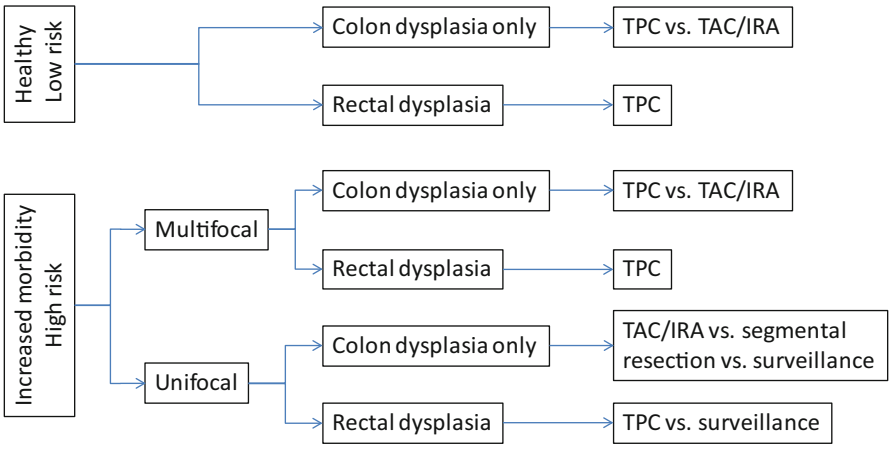

Fig. 6.1 Surgical options for ulcerative colitis patients with dysplasia found on colonoscopy. *IPAA* ileal pouch-anal anastomosis, *IRA* ileorectal anastomosis, *TAC* total abdominal colectomy, *TPC* total proctocolectomy

6.3.1 Abdominoperineal Total PC

Abdominoperineal total PC is the most definitive treatment for the eradication of undiagnosed synchronous dysplasias and/or carcinomas and the prevention of subsequent metachronous lesions in UC. It allows the resection of synchronous colonic and rectal dysplasia/cancer and avoids the development of metachronous colonic and rectal lesions. It also obviates the need for further colonoscopic surveillance. However, patients must accept a permanent stoma and the postoperative complications are significant, including urinary and sexual dysfunction or a nonhealing perineal wound.

Although this procedure is not an attractive option for patients with comorbidities or for those wanting to preserve anal function, it is indicated for patients with advanced rectal and anal canal cancer or for patients with poor anal sphincter function, such as the older postpartum female. These patients will also require an end ileostomy or a continent Kock ileal pouch.

6.3.2 Segmental/Partial Resection

There is limited debate regarding segmental colectomy in the treatment of lesions in patients with UC in long-standing remission. The indication for the procedures considers the difficulty of further PC and IPAA after lymphadenectomy or adhesions at the target surgical site.

Segmental colectomy is a short operative procedure and maintains continence, but most patients will later require not only further medication but also excision and

colectomy and ileostomy. Moreover, a right-sided colo-anal anastomosis is unsuitable for the treatment of left-sided UC [50]. Thus, in general, partial resection of the colon should be avoided because of the high frequency of occult carcinomas and multifocal carcinogenesis. Schwarz et al. [51] reported the case of a patient who underwent a left hemicolectomy and a mucosal proctectomy but then had a macroscopic recurrence of the colitis within 2 months postoperatively and eventually required excision of the remaining colon and an end ileostomy. This suggests that the risk of UC relapse in the residual colon must be taken into account, even if the right side of the colon seems to be in remission.

Patients with UC-associated CRC have a twofold higher mortality than patients with sporadic CRC [52]. Whether segmental or partial resection is the optimal procedure for UC patients with sporadic cancer remains questionable.

6.3.3 Total Abdominal Colectomy with Ileorectal Anastomosis

The cumulative probability of total abdominal colectomy with ileorectal anastomosis (IRA) after 10 years of UC is about 50 %. Total excision was performed following the detection of dysplasia in 5.9 % of these patients [53] and is no longer an acceptable procedure for patients with UC. Although UC is generally considered to always involve the rectum and in some patients also the more proximal portions of the colon, albeit in a diffuse and non-segmental fashion, rectal sparing has been documented [53–57]. If the colitis is totally quiescent or shows rectal sparing, total abdominal colectomy with IRA may be an option for UC patients with a single cancer in the colon. However, since most colectomy specimens with an absence of macroscopic activity show histologic features of chronicity or activity [58], these patients should be monitored for a relapse of proctitis.

The indication of low anterior resection for patients with quiescent UC and rectal cancer or dysplasia should be considered very carefully, because further PC and IPAA would be difficult after this procedure. In addition, patients undergoing total abdominal colectomy with IRA and treated postoperatively with immunomodulators or biologics have a risk of a relapse of inflammation in the residual rectum. Thus, the prognosis, and especially the risk of cancer in the residual rectum, after IRA in patients with UC-associated cancer is a concern. Among patients who received an IRA, regardless of the indication, the estimated cumulative cancer risk after a disease duration of 20 years is 2.1–20.0 % [59–63]. The high long-term risk of cancer after total abdominal colectomy with IRA suggests that this procedure is an interim solution in younger patients. However, IRA with a close follow-up still plays a major role in treating UC patients because it is an easier surgical procedure than IPAA, has excellent functional results, shorter hospitalization, and, importantly, fewer severe complications, unlike in IRA [61].

A particular indication of IRA for UC-associated cancer is a non-obstructing tumor located above the pelvic floor with remote metastases in remission. In the case of an advanced tumor causing obstruction, then a primary colectomy and IRA with a covering ileostomy is advisable.

6.3.4 Subtotal Colectomy

Subtotal colectomy (STC) with end ileostomy and rectal stump pouch are less ideal options because of the retained rectum, which poses a continued cancer risk. However, STC was shown to be a safe treatment option for patients satisfied with an ileostomy or for those with comorbidities that make them ineligible for other procedures or who do not choose to undergo later pelvic pouch surgery. Nonetheless, the potential for the proliferation of residual dysplastic cells or malignant change within the rectal stump in patients who have undergone STC with rectal stump preservation for UC-associated CRC is of serious concern. In addition, whether the potential for malignancy in the rectal stump of STC patients with UC-associated CRC outweighs the morbidity associated with complete proctectomy is difficult to determine. The rate of cancer occurrence later on was shown to be low (1.4 %) in one study [62] but eightfold higher in another [64]. PSC and disease duration until STC were shown to be significant risk factors for rectal stump cancer in a closed rectal stump after STC [65]. Thus, considering the risk of rectal cancer, the low success rate of long-term rectal preservation, and the safety of surgery, a more aggressive approach to early complete proctectomy is recommended in this situation. If this is not possible, patients treated with STC should be followed with close endoscopic surveillance of the closed rectal stump.

6.3.5 Total Proctocolectomy with IPAA

IPAA by ileal J pouch, first described in 1980, is now the gold standard surgical procedure for UC refractory to medical treatment [66]. The long-term quality of life of these patients after this procedure is excellent and the level of fecal continence is satisfactory [67–69]. However, this procedure also has several technical difficulties such as mesenteric lengthening of the pouch [70, 71] and mucosal proctectomy [72]. For surgeons, extensive experience is required to obtain acceptable results [73]. Patients with refractory UC who suffer complications after PC have a poor quality of life [74]. Thus, a double-stapled anastomosis without mucosal proctectomy is the preferred procedure, as there are fewer anastomotic complications and superior rectal continence is achieved; however, a cuff of rectal mucosa is retained, which is the main concern as well as the main argument of opponents of the double-stapling technique. Whether with or without mucosal proctectomy, IPAA is indicated for any colonic or rectal lesion in the surgically fit patient who

has unifocal or multifocal dysplasia and refuses a stoma. Relative contraindications of IPAA for UC-associated neoplasias are preoperative incontinence/poor anal sphincter tonus, severe backwash ileitis suggesting Crohn's disease, and very low rectal or anal dysplasia that threatens the sphincters.

However, the use of a stapled anastomosis without mucosal proctectomy in patients with UC-related dysplasia or cancer remains controversial because of the risk of developing synchronous or metachronous neoplasias in the retained anal transitional zone (ATZ) mucosa. Although an association has yet to be reported between dysplasia and any the following: age, sex, preoperative length of disease, use of a double- vs. single-staple technique, or anastomotic distance from the dentate line [75], the risk of cancer can be reduced by ensuring that the minimal length of rectal columnar mucosa is retained. It is therefore recommended that, in carrying out a stapled IPAA, the anastomosis is performed at the anorectal junction, about 1–1.5 cm above the dentate line, because of the deterioration in anorectal function [76]. Additionally, this procedure is indicated for patients with UC and right-sided colon cancers who require lymph node dissection along the superior mesenteric vein and excision of the marginal arcade of the ileocolic artery, because an insufficient extension of the ileal pouch to the anus precludes a hand-sewn IPAA with mucosectomy.

Stapled IPAA has also been advocated in patients with UC associated with coexisting neoplasia [77, 78]. In these cases, long-term surveillance to monitor dysplasia is recommended; if repeat biopsy confirms persistent dysplasia, ATZ excision with a neoileal pouch-anal anastomosis should be performed [78]. However, restorative PC with mucosectomy does not necessarily eliminate the risks, as after this procedure cancer can occur in a residual ATZ [79, 80]. Thus, in patients with long-standing ileal pouches even after mucosectomy of ATZ, and especially in cases in which dysplasia or cancer is detected in the PC specimen, routine long-term endoscopic surveillance is recommended.

There are many reported cases in the indexed medical literature of carcinoma arising after stapled IPAA for UC [79]. In some studies, the incidence of dysplasia in the ATZ at the time of total colectomy was 2.5–5 %, and duration of UC and patient age at colectomy were significant risk factors [81, 82]. In these cases, mucosal proctectomy is the definitive procedure for patients with preoperatively detected dysplasia in the ATZ.

The incidence of dysplasia after stapled IPAA is 3.0–4.5 % [75, 76, 83]. The development of cancer in the ATZ after stapled IPAA without mucosectomy has been reported [76, 84, 85] and was shown to be significantly associated with a preoperative pathologic diagnosis of UC with concurrent dysplasia or cancer [75]. Based on these data, mucosal proctectomy and hand-sewn IPAA are strongly recommended for patients with neoplasia, especially those with cancer or HGD outside the ATZ [75, 86].

For the reasons stated above, in young patients with UC-associated cancer, mucosal proctectomy with IPAA is recommended, whereas for older patients, particularly those with lower rectal cancer who will accept a permanent stoma, total PC may be proposed. Patients older than 50 years have a significantly higher

rate of concurrent dysplasia and malignant degeneration than younger patients, probably because of a longer duration of disease [87]. In these cases, restorative PC with mucosal proctectomy may reduce this risk by eliminating all of the colorectal mucosa.

Branco et al. [88] reported a case in which adenocarcinoma arose in an ileal pouch after IPAA with mucosal proctectomy performed using a cavitron ultrasonic surgical aspirator (Excel, Covidien, Boulder, CO) for UC. This method was introduced to simplify and optimize IPAA with mucosectomy and has been shown to shorten the operative time and reduce blood loss [89]. Its use, however, may increase the number of pathology specimens made uninterpretable on account of tissue ablation. Another ultrasonically activated scalpel (Harmonic; Ethicon Endo Surgery, Johnson & Johnson Medical SPA, Somerville, NJ) also shortened the operative time, decreased blood loss, and was shown to be useful for restorative PC [72]. There has been no report of adenocarcinoma arising in an ileal pouch after mucosectomy performed using this device.

6.3.6 Endoscopic Resection

The ALMs seen in UC patients are similar to those observed in non-UC patients that have been treated by standard polypectomy. This method is associated with little risk of subsequent malignancy on follow-up [42, 44, 90, 91].

An accurate pathologic diagnosis is very important for distinguishing among the different pathologic entities, given the different therapeutic consequences, such as endoscopic polypectomy for ALM and potential PC for DALM. New and emerging endoscopic imaging techniques, such as chromoendoscopy, magnification endoscopy, and confocal laser endomicroscopy, provide a more accurate diagnosis. Endoscopic resection of an ALM allows confirmation of the biopsy-based adenoma diagnosis and the exclusion of a DALM [91]. However, the endoscopic resectability of a lesion is more important than whether it is an ALM or a DALM [92]. The basic rules for the detection of neoplasia [93] (Table 6.1) should be taken into account and applied in accordance with international guidelines [95–97].

Only a few studies have examined the clinical outcomes of DALMs resembling ALMs that are removed with endoscopic polypectomy, but the safety and efficacy of endoscopic resection have been evaluated [93, 94, 98]. Since DALMs, in particular those with a polypoid mass, are an indicator of a high likelihood of the presence of synchronous or metachronous neoplasia, endoscopic resection is not appropriate [22, 40].

Table 6.1 Basic rules for detecting neoplasia in patients with UC

1. Consult with experienced gastroenterologist
2. Endoscopic and bioptic control in remission phase
3. Examination outside routine schedule without time limitation
4. Ileocolonoscopy with special focus on the detection of DALMs and step (quadrant) biopsies from the rectum to the cecum in 10-cm intervals (sigmoid and rectum: quadrant biopsies at 5-cm intervals)
5. ALMs with low-grade intraepithelial neoplasia and clear-cut margins can be resected endoscopically
6. Consult with experienced histopathologist who has all clinical and endoscopy data readily available
7. Second opinion recommended in cases of histological diagnosis of neoplasia

From [94]

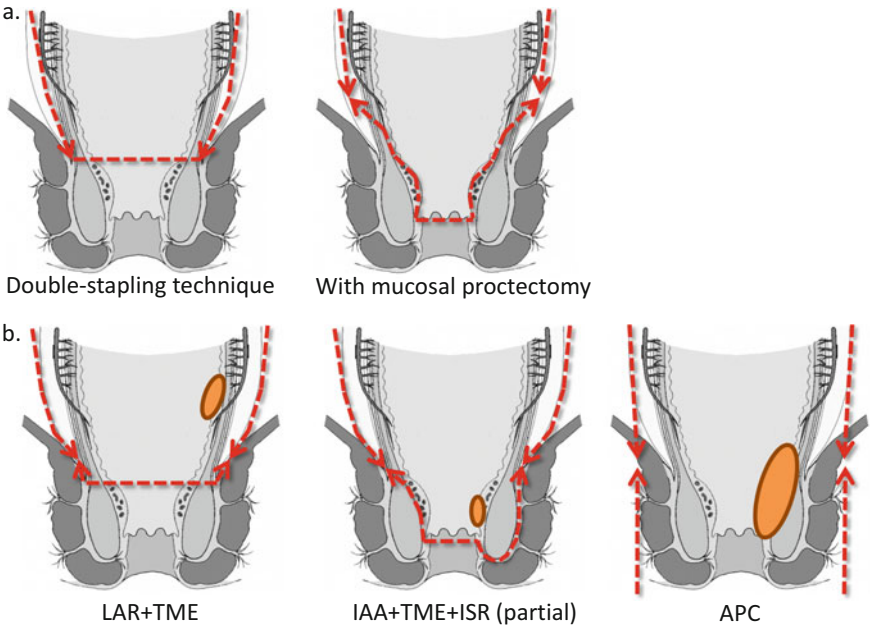

Fig. 6.2 Perianal resection line. Ileal pouch-anal anastomosis (IPAA) for ulcerative colitis (UC) (**a**), UC-associated low rectal neoplasia (**b**). *TME* total mesorectal excision, *LAR* low anterior resection, *IAA* ileoanal anastomosis, *ISR* intersphincteric resection, *APC* abdominoperineal total proctocolectomy

6.3.7 Perianal Resection Line for Rectal and Anal Canal Neoplasia

In an IPAA performed in a patient with UC without colorectal neoplasia (Fig. 6.2a.), the mesorectum is resected on the inside, close to the rectal wall, to preserve autonomic nerve function. In patients with UC-associated low rectal

Table 6.2 Indication and procedure for mesorectal excision in UC patients with rectal and anal canal cancer

Tumor status	Procedure
T1	IPAA with mucosal proctectomy (TME is recommended, taking into consideration the risk of a deeper level of T2)
Deeper level of T2 and not lower than 4 cm from the anal verge	IPAA with mucosal proctectomy and TME
Deeper level of T2 and lower than 4 cm from the anal verge	IPAA with mucosal proctectomy and TME ± ISR or APC
Deeper level of T3 or positive for lymph node metastasis	Consider preoperative chemoradiotherapy followed by APC with TME

IPAA ileal pouch-anal anastomosis, *TME* total mesorectal excision, *ISR* intersphincteric resection, *APC* abdominoperineal total proctocolectomy

neoplasia, total mesorectal excision is required in performing an IPAA (Fig. 6.2b). The choice of operative procedure depends on the depth of the tumor and its distance from the anal verge (Table 6.2). Regarding IPAA with intersphincteric resection, there are no data on postoperative anal function from a large number of cases. Thus, consensus on this procedure is lacking. Depending on curability, however, it should at most be confined to a partial intersphincteric resection (Fig. 6.2b).

6.4 Immunomodulators

Medical therapy for UC has advanced dramatically in the last decade, which has led to discussions of the pros and cons of immunomodulators or biologics for UC patients with malignant disease. Previous studies and guidelines showed that patients administered immunomodulators or biologics do not have a higher risk of new cancer development [99]. Anti-TNF antibodies have been linked to a risk of cancer recurrence in rheumatoid patients, thiopurine to a risk of cancer recurrence in transplant patients, and calcineurin inhibitor to a risk of hepatocellular carcinoma recurrence in liver transplant patients [100–102]. However, a meta-analysis of 74 random controlled trials found that anti-TNF therapies are not related to the short-term clinical emergence of cancer [103]. Nonetheless, a relapse residual lesion is not a rare occurrence after segmental/partial resection; thus, in these patients with advanced cancer, the restricted use of immunomodulators or biologics should be considered.

6.5 Prognosis

6.5.1 Neoplasia in an Ileal Pouch

Previously, cancer of the ileal mucosa was reported in patients who underwent a Brooke ileostomy [104–107] and in those with a Kock pouch [108], but the natural history and prognosis of pouch dysplasia or cancer are poorly understood. Although inflammation, villous atrophy, and colonic metaplasia have been observed within the mucosa of ileal pouches after IPAA, dysplasia may also develop, but the incidence is <0.02 % 20 years after IPAA [109].

In their study of pouch-related adenocarcinoma, Selvaggi et al. [64] showed a pooled cumulative incidence of 0.33 % 50 years after the diagnosis and 0.35 % 20 years after IPAA in a systematic review of the meta-analyses of the literature of pouch-related adenocarcinoma in patients with an IPAA for UC. In that study, one-third of the adenocarcinomas arose from the pouch as a whole and the remainder from the anorectal mucosa [64].

Derikx et al. [110] used the National Registry from 1991 to 2012 to identify 1200 patients with IBD and IPAA; 25 (1.83 %) developed pouch neoplasia, including 16 adenocarcinomas. The cumulative incidence of pouch neoplasia at 5, 10, 15, and 20 years was 1.0 %, 2.0 %, 3.7 %, and 6.9 % for pouch neoplasia and 0.6 %, 1.4 %, 2.1 %, and 3.3 % for pouch carcinoma [110] (Fig. 6.3). A history of colorectal neoplasia was the only risk factor associated with pouch neoplasia. Hazard ratios were 3.76 (95 % CI: 1.39–10.19) for prior dysplasia and 24.69 (95 % CI: 9.61–63.42) for prior carcinoma [110]. Another systematic review similarly concluded that neoplasia in the colectomy specimen was the strongest risk factor (odds ratio = 8.8; 95 % CI: 4.61–16.80) [64].

Malignant transformation of the ileal pouch mucosa may occur even in the absence of backwash ileitis or a previous history of cancer [111, 112], as determined in biopsies from the ileal pouch mucosa obtained at least 1 year after the newly formed pouch that was influenced by fecal flow [113]. Chronic inflammation of the ileal mucosa such as occurs with preoperative backwash ileitis and postoperative pouchitis in UC has also been linked to the sequence of malignant transformation [114–117]. An abnormal lesion of the ileal pouch mucosa was shown to have a high risk of adenocarcinoma 20 years or later after the initial IPAA [118].

PSC-IBD patients are at increased risk of colorectal neoplasia [38], but the development of pouch neoplasia in PSC-UC patients following IPAA is unclear. Imam et al. [119] conducted a retrospective chart review of 65 patients with PSC and IBD who underwent colectomy with IPAA followed by pouch surveillance between 1995 and 2012. The cumulative 5-year incidence of pouch neoplasia was 5.6 % (95 % CI, 1.8–16.1 %). Based on this short-term follow-up, they concluded that a frequent surveillance of the pouch was an unnecessary practice in PSC-IBD patients. However, it is recommended that patients with these risk factors be followed by endoscopy and random biopsies for the rest of their lives. If a pouch-

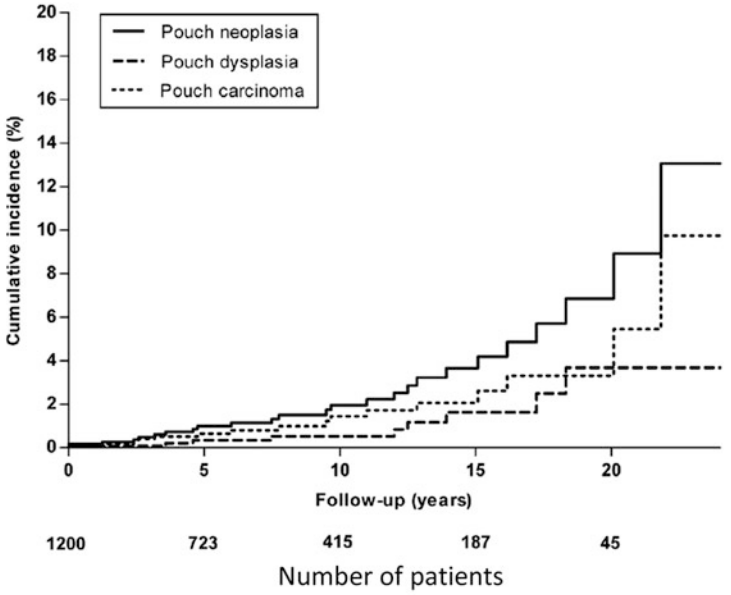

Fig. 6.3 Cumulative incidences of pouch neoplasia (both carcinoma and dysplasia), pouch carcinoma, and dysplasia (From [110])

related adenocarcinoma is detected during these examinations, abdominoperineal excision is recommended.

6.5.2 Outcome of Colorectal Cancer in UC

There have been a few reports based on small series that examined the outcome of patients with UC and CRC [12, 120–123]. From a functional aspect, among cancer patients who received an IPAA, no significant differences could be found between those with UC-associated CRC and those with UC without CRC [124]. For UC-associated CRCs, as for non-colitic cancers, histologic stage, site, and mucin content of the tumor are the most important variables determining postoperative survival [49].

A 20-year follow-up study of IBD-related CRC from the Mayo Clinic compared patients with sporadic CRC with age- and sex-matched patients with IBD-related cancers. In the latter group, the tumors were more proximally located, with only 55 % distal to the splenic flexure, compared with 78 % among patients with sporadic CRC [125]. However, compared with sporadic tumors, IBD-related CRC was more often in an advanced stage and more likely to have a mucinous component [125]. Yet, no differences were found in the overall survival of patients with sporadic CRC and those with IBD-related CRC [125].

Heimann et al. [126] showed that the 5-year survival rate was significantly worse for patients with non-diploid tumors (76 % vs. 32 %). When stratified by stage, only patients with Dukes' C lesions had a significant difference in survival for diploid vs. non-diploid tumors. Multivariate analysis showed that Dukes' classification was the best prognostic indicator, followed by tumor differentiation and DNA ploidy. Tumor location, colloid content, number of cancers, duration of disease, and patient age and sex did not correlate with the prognosis [126].

A retrospective review of 1642 UC patients by Kavanagh et al. [127] showed that patients who undergo surgery for UC-associated CRC ($n = 22$) have less favorable short-term outcomes but present at a less advanced stage and have a more favorable long-term prognosis than similar patients with CRC and Crohn's disease. The overall 5-year survival was significantly better in the UC group than in the group with Crohn's disease (41 % vs. 29 %; $P = 0.04$).

Watanabe et al. [128] showed that in a group of 108,536 CRC patients, the 169 with UC-associated CRC had a poorer survival than patients with sporadic CRC (43.3 % vs. 57.4 %; $P = 0.0320$) for stage III disease but not for early-stage disease. The authors concluded that the detection of UC-associated CRC at an early stage results in similar postoperative outcomes as those of patients with sporadic CRC. A Danish population-based study also compared patients with UC-associated CRC ($n = 279$) and those with sporadic CRC ($n = 71{,}259$). Cancer stage and rates of lymph node and distant metastasis were similar between the two groups, but the overall mortality rates at 1 and 5 years after cancer diagnosis were higher in UC-associated CRC than in sporadic CRC (OR = 1.24; 95 % CI: 1.02–1.51 and OR = 1.17; 95 % CI: 1.01–1.36, respectively) [129]. Other population-based studies showed that patients diagnosed with UC-associated CRC at age <60 years had a worse outcome [130, 131], which, according to Shu et al. [131], was more pronounced in males.

6.5.3 Radiation/Chemotherapy

Although locally advanced rectal cancer requiring multimodality therapy is uncommon in patients with UC, the functional outcome of patients with UC-associated CRC who received adjuvant chemotherapy was shown to be very good if the appropriate surgical technique and chemotherapy protocol were selected [86].

Preoperative chemoradiotherapy (CRT) and total mesorectal excision with or without intersphincteric excision are the current treatment choices for patients with lower rectal cancer. This approach was shown to optimize oncologic outcome and to maintain anorectal function [132]. By contrast, pelvic radiation administered prior to IPAA is associated with poor pouch outcomes for UC patients [86, 133, 134]. In fact, external beam radiation to treat cancer is problematic in UC patients, especially because the small bowel has a lower tolerance than the large bowel [135]. Thus, whether adjuvant CRT increases postoperative complications remains controversial [133, 136].

In patients with cancer located in the ATZ and close to the internal sphincter, restorative PC and partial intersphincteric resection may be indicated [136], whereas preoperative CRT has a negative impact on sphincter function [136–138]. A recent report identified preoperative CRT as a risk factor for impaired anal function after intersphincteric resection [139]. CRT followed by IPAA and partial intersphincteric resection may be even more destructive in terms of postoperative anal function, with several studies showing better outcomes than colonic J pouch reconstruction for lower rectal cancer [140–142]. Previous reports demonstrated a high tolerance of preoperative CRT and pouch surgery with minimum intersphincteric resection [142, 143]. Overall, because prognosis seems to be related to cancer stage, the oncologic benefits and pouch functional outcomes should be carefully balanced before pelvic radiation prior to IPAA is considered [134].

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Chapter 7
Surgical Treatment for Colorectal Cancer in Crohn's Disease

Hiroki Ikeuchi, Motoi Uchino, Toshihiro Bando, Kei Hirose, Nobuyuki Hida, and Shiro Nakamura

Abstract Cancer associated with Crohn's disease (CD) has shown a recent increasing trend. However, early detection is difficult due to an absence of characteristic symptoms, and differentiation from CD-related symptoms is challenging. For effective surgical treatment, it is necessary to determine malignancy according to the type of lesions, such as small intestinal, colonic, and anorectal. Intestinal cancer is less frequent and difficult to reveal prior to surgery, as its final diagnosis is often made based on perioperative or postoperative pathological examination results. For colonic lesions, final diagnosis is obtained in a similar manner. Furthermore, outcome is reported to be poor, as most cases are progressing at the time of diagnosis.

It remains inconclusive whether patients with colonic cancer and CD with colonic dysplasia as a complication should be treated by segmental resection or total colectomy as in ulcerative colitis (UC) cases. The prognosis of cancer associated with anorectal lesions is poor, though some reports have suggested that it can be improved by preoperative chemoradiotherapy. For cancer associated with anorectal lesions, rectal amputation is inevitable. However, for those cases with extensive lesions around the anus, sacroabdominal rectal amputation, for which the surgery is started from the anal side in the jackknife position and later changed to another posture, is frequently more advantageous than ordinary abdominoperineal rectal amputation. The important complication after rectal amputation is persistent perineal sinus (PPS). Vacuum-assisted closure (VAC) is sometimes performed but satisfactory results are yet to be reported.

Furthermore, it is important to establish a method of surveillance for early detection.

Keywords Crohn's disease • Surgical treatment • Colorectal cancer

H. Ikeuchi (✉) • M. Uchino • T. Bando • K. Hirose • N. Hida • S. Nakamura
Department of Inflammatory Bowel Disease, Hyogo College of Medicine, 1-1 Mukogawa-Cho, Nishinomiya, Hyogo 663-8501, Japan
e-mail: ikeuci2s@hyo-med.ac.jp

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7.1 Introduction

The occurrence of cancer in CD was not appreciated until many years after the classic description of "regional enteritis" in 1932. Recently, it has been recognized that CD carries an increased risk for malignancy [1, 2]. Three types of gastrointestinal carcinomas occur more frequently in patients with CD than in the regular population: small bowel cancer, colorectal cancer, and carcinoma arising from perianal fistula [2–6]. The presence of anal carcinoma in CD is clearly associated with long-standing perianal fistula [7]. Especially, physicians should have a high level of suspicion of cancer in patients with long-standing perianal CD who have a change in symptoms.

Preoperative, operative, and postoperative care require expertise in CD and a concomitant knowledge of oncologic surgery.

7.2 Location of Cancer in CD

Operative procedures depend on the location of the tumor. It is said that the localization of a tumor differs geographically. When considering geographic variations, the risk of colorectal cancer associated with CD is significantly higher in North America and the United Kingdom in comparison to Scandinavian countries [8]. These results may represent the genetic, dietary, or environmental differences between the countries. Stahl et al. found in their series that only 17 % ($n = 4$) of cancers in CD patients were located to the rectum which was much lower than in sporadic cancer (38 %) [9]. On the other hand, 59 % ($n = 14$) were located to the ascending and transverse colon in the CD patients which was significantly higher than in sporadic cancer (28 %). Kersting et al. reported previous studies that showed that 39–50 % of CD-associated tumors are located in the rectum [5, 10–12]. In their study, the majority of CD-associated tumors were located in a segment of the intestine that was easily accessible to endoscopic examination.

On the other hand, Mizushima et al. reported that based on the fact 34 of 44 colorectal cancers (77.3 %) in Japanese patients with CD arose in the sigmoid colon, rectum, and anal canal/fistula [13]. There may be genetic and environmental factors associated with developing colorectal cancer in patients with CD. Table 7.1 shows the location of cancer in our CD patients. Twenty-two of 32 (68.8 %) patients are located with anorectal lesions.

Table 7.1 Location of cancer

Location	No.
Fistula	4
Enteroenteric	3
Enterocutaneous	1
Intestinal tract	28
Ileum	2
Cecum	2
Descending colon	1
Sigmoid colon	1
Rectum	6
Anal canal	8
Anal fistula	8

7.3 Preoperative Preparation

7.3.1 Specific Medical Problems

Anemia, hyperglycemia, and electrolyte abnormalities should be discovered and remedied prior to operation.

7.3.2 Stoma Site Marking

In a patient with rectal amputation, consultation with an enterostomal therapist should be made to assist in the placement of the proposed stoma. Ideally the site should be located over the rectus muscle on a flat area from deep skin folds and bony prominences. The surface of the abdomen should be evaluated in the supine, sitting, and standing positions as this will often demonstrate skin folds and creases not evident in the other position. Finally, the patient's belt line is determined and every effort is made to place the stoma below it.

7.3.3 Preoperative Antibiotics

Intravenous prophylactic antibiotics should be administered 1 h prior to surgery so that maximal tissue antibiotic levels are achieved at the time of the skin incision.

7.4 Preoperative Examination

The presence of a complex fistula, an associated stricture, and perineal pain prevents a thorough examination of the anus and perineal areas, thus making diagnosis of a concomitant carcinoma difficult. Devon et al. reported that 14 patients who complicated cancer of anus all had multiple imaging studies, including magnetic resonance imaging (MRI), CT, and endorectal ultrasound, but none of these studies were diagnostic of carcinoma [14]. The diagnosis of cancer was made preoperatively in 10 of 14 patients, usually after multiple biopsies. In four patients, despite multiple tissue biopsies, the diagnosis was made intraoperatively ($n = 2$) or postoperatively ($n = 2$) [14].

The outcome is the same as in sporadic cancer at a corresponding stage; however, the prognosis is often poor due to the advanced stage at diagnosis. There are no formal guidelines for screening and surveillance of cancers associated with CD in the lower rectum and perianal regions. Friedman reported that if the endoscopist is unable to pass the stricture and perform surveillance with a standard pediatric endoscope, a barium enema or CT colonography should be considered to evaluate the proximal colon, with possible referral to an expert center [15].

7.4.1 MRI Examination

For anorectal cancer, pelvic MRI is the best method for examining cancer localization and invasion, as well as its positional relationship with surrounding organs. An anal fistula carcinoma related to mucinous cancer frequently forms mucus retention; thus multilocular cyst-like findings are frequently observed in T2-weighted MRI images. Figure 7.1 shows T2-weighted MRI findings of a mucinous cancer case, with multilocular cysts indicated by an arrow.

7.4.2 FDG-PET Examination

Some recent reports indicated the potential of FDG-PET to assess CD activity [16–18]. On the other hand, there is no report of the potential of FGD-PET to assess CD-associated malignant tumors. In our study, we performed FDG-PET with four patients prior to the operation, and the results indicated that two were positive and two were negative. Based on our limited experience, the accuracy rate for FDG-PET is not high, possibly because of the high rate of mucinous cell-type carcinoma in CD-associated cancer. In addition, Whiteford et al. reported that the sensitivity of FDG-PET for detecting mucinous carcinoma was lower than that for nonmucinous cancer [19].

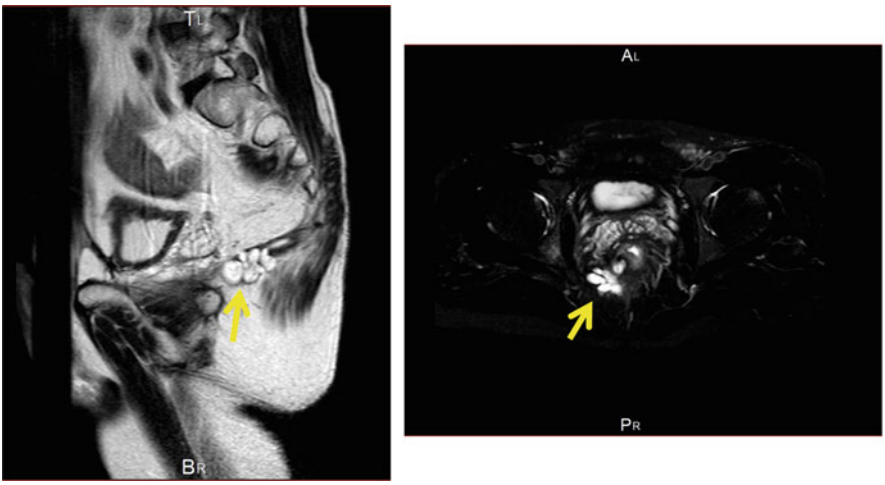

Fig. 7.1 T2-weighted images in patient with mucinous carcinoma. Multilocular cysts indicated by an arrow

7.4.3 Curettage of the Fistulous Tract

Severe chronic complicated perianal disease in patients who have CD seems to be associated with an increased risk for cancer in the lower rectum and anal canal. Laurent et al. noted that a high degree of suspicion for carcinoma must be considered during a rectal examination under anesthesia with biopsy, curettage, or brushing of the fistulous tract recommended [20]. The case which performed curettage of the fistula under anesthesia is shown in Fig. 7.2. The outflow of mucus is shown from a primary lesion.

7.5 Preoperative Treatment

7.5.1 Preoperative Chemoradiotherapy

No conclusions can be drawn regarding the efficacy of adjuvant chemoradiation in CD patients with fistula-associated anal adenocarcinoma because of the small population analyzed and the retrospective nature of the present study. Mucinous rectal adenocarcinoma has been associated with a lower response to chemoradiation than nonmucinous rectal cancer [21–23]. Sengul et al. compared the outcome after preoperative chemoradiation in 16 patients with mucinous rectal cancer and 55 patients with nonmucinous rectal cancer. Patients with mucinous tumors were found to have significantly more advanced T stages after chemoradiotherapy. Only

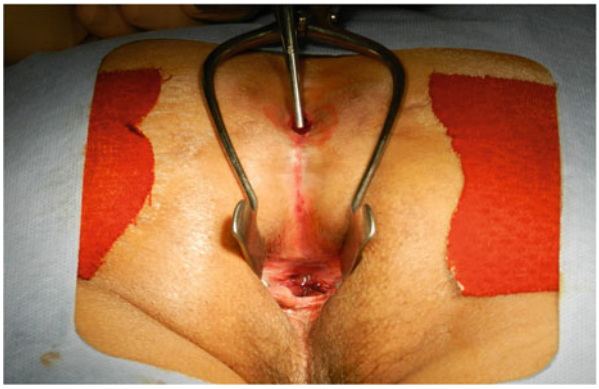

Fig. 7.2 Curettage of the fistula under anesthesia. This patient was diagnosed with mucinous adenocarcinoma

18 % of patients with mucinous cancer compared to 74 % of patients with nonmucinous cancer had a shift toward earlier T and N stages [21].

On the other hand, Wolfgang et al. reported that they had good results with combined neoadjuvant chemoradiation; all seven of their patients who received this treatment had a complete response, and they believe that neoadjuvant chemoradiation may play an important role in the treatment of locally advanced disease [24].

7.5.2 Case Presentation

Figure 7.3 shows the CD patients with complicated lower rectal carcinoma. He was 31 years old, and he had 15 years CD history. His preoperative pathological diagnosis was mucinous carcinoma. He was performed preoperative chemoradiotherapy and performed abdominoperineal rectal resection. Details regarding the per-treatment MRI examination, postoperative resected specimen, and pathological examination for that patient are provided in Fig. 7.3. He subsists without local recurrence 6 years after the operation.

7.6 Surgical Treatment

The objective of surgery for cancer in CD is resection of the cancer for cure or, when indicated, palliation and removal of associated or discontinuous segments of inflammatory disease when necessary. Surgical resection is generally accepted as the basic step in the treatment of these patients. Information on the adjuvant role of chemotherapy or radiotherapy is limited. Advanced rectal carcinomas are usually treated with preoperative pelvic irradiation. In patients with inflammatory bowel

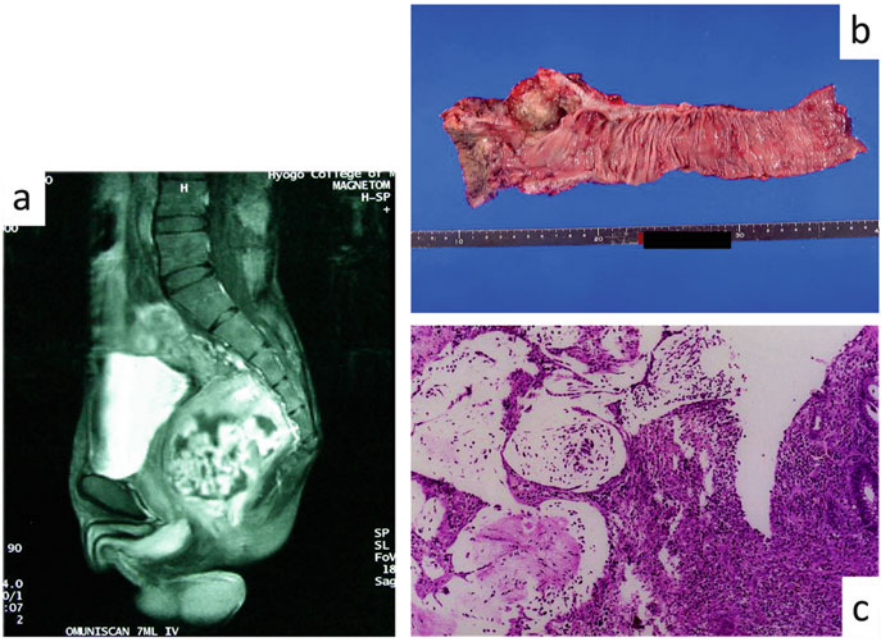

Fig. 7.3 CD-associated lower rectal carcinoma. (**a**) Preoperative MRI examination showing a tumor occupying most of the pelvic cavity. (**b**) Necrotic tumor specimen resected from the lower rectum. (**c**) Pathological examination results of a mucinous tumor with inflammatory cells. No malignant cells were found in this specimen

disease, however, this treatment produces an increased risk for severe gastrointestinal complications [25].

7.6.1 Small Bowel Cancer

7.6.1.1 Characteristic

There is a strong association between CD and small bowel cancer. The increased relative risk of small bowel cancer has been reported to be between 15.6 and 114.5 in comparison to the general population [26–30]. Cancer of the small intestine occurring in combination with CD is not as common as cancer of the large intestine. In addition, since cancer of the small intestine developing in patients with CD occurs in infected regions, it is very difficult to detect the disease at an early stage. This is because X-ray images of small intestinal cancer are similar to the images of strictures in patients with CD.

Making a definitive diagnosis of combined cancer was not possible before surgery, and the definitive diagnosis is obtained based on an intraoperative or

postoperative pathological diagnosis. Palascak et al. reported that small bowel cancer was difficult to diagnose and was made preoperatively in only 1 of 20 patients who had CD as compared with 22 of 40 patients who had sporadic adenocarcinoma [31].

If we encounter such cases, we worry about whether to perform the reoperation or not, because the basic of surgery differs from CD and cancer.

7.6.1.2 Operative Procedure

Segmental resection is the performed surgical therapy for small bowel cancer in segmental CD. In patients with multiple small bowel strictures, concomitant strictureplasties should be performed in addition to the resection of the malignant stricture. Each stricture should be biopsied with frozen section evaluation to rule out the presence of synchronous cancers before a strictureplasty is carried out [32].

7.6.1.3 Case Presentation

A male developed diarrhea and fever at the age of 18 years and was diagnosed with CD in a detailed investigation. He had poor compliance to the prescribed drug therapy and visited the hospital on an irregular schedule. At the age of 34, he was admitted to our hospital for close examination of repeated ileus symptoms that had begun about 4 months prior to treatment. As the ileus symptoms became aggravated, a long tube was inserted. Figure 7.4 shows findings obtained in a series of images of the small bowel, in which a lesion suggestive of internal fistula was noted near the terminal ileum.

Surgery was performed to remove the segment. During the laparotomy, multiple nodes were found in the peritoneal cavity and subjected to an intraoperative pathologic examination, which led to a diagnosis of peritoneal dissemination of a poorly differentiated adenocarcinoma. The lesion was surgically removed and an artificial anus was created on the opening side. The resected specimen is shown in Fig. 7.5. Cancer invasion was observed up to the serous surface and distention of the

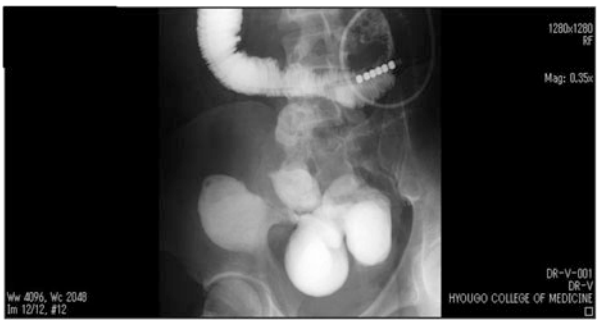

Fig. 7.4 Preoperative small intestinal examination

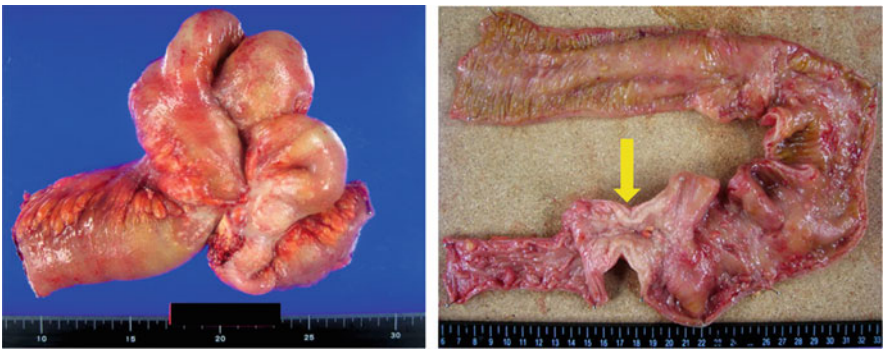

Fig. 7.5 Resected specimen in CD patient with small intestinal cancer. A lesion suggestive of internal fistulation was noted near the terminal ileum

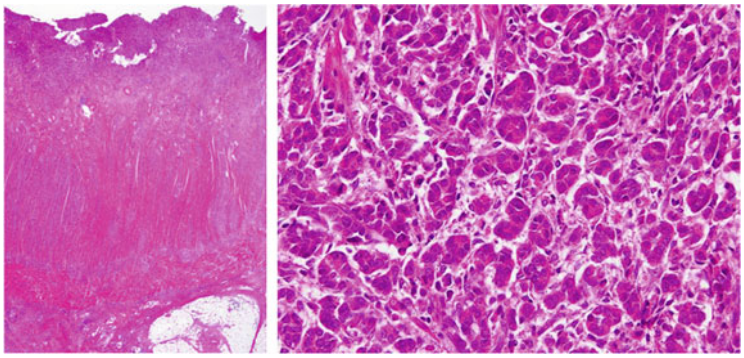

Fig. 7.6 Postoperative pathological findings. We determined that this was a case of poorly differentiated adenocarcinoma

gut on the opening side. We determined that this was a case of poorly differentiated adenocarcinoma (Fig. 7.6).

7.6.2 Colon Cancer

7.6.2.1 Segmental Resection

Segmental resection is the performed surgical therapy for colonic cancer in segmental CD.

7.6.2.2 Subtotal Colectomy

Subtotal colectomy is the procedure of choice in the presence of CD of the colon with malignant degeneration and sparing of the rectum. Following an abdominal

colectomy, long-term surveillance with yearly endoscopy and biopsies of the remaining rectal segment is essential.

7.6.2.2.1 Case Presentation

A 30-year-old woman underwent complete resection of the colon and an ileostomy for multiple colonic lesions and a rectovaginal fistula. Thereafter, there was no close examination of the rectum as no aggravation of the rectovaginal fistula was noted. During a uterus cancer screening examination at the age of 40, an adenocarcinoma was found. She then came to our hospital for careful investigation of the remaining rectum, in which a carcinoma was found in a rectovaginal fistula on the rectal side. She underwent amputation of the remaining rectum. The resected specimen is shown in Fig. 7.7.

7.6.2.3 Total Proctocolectomy (TPC)

This procedure is generally performed for colonic cancer patients with pancolitis or with segmental colon and rectal disease or with colon and severe perianal disease.

7.6.2.4 The Surgical Treatment of CD-Associated Dysplasia

It remains unresolved whether total proctocolectomy is required for colorectal cancer or dysplasia in CD as it is in UC or whether segmental resection might be adequate [33]. 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 [33]. In the patients with multifocal colonic

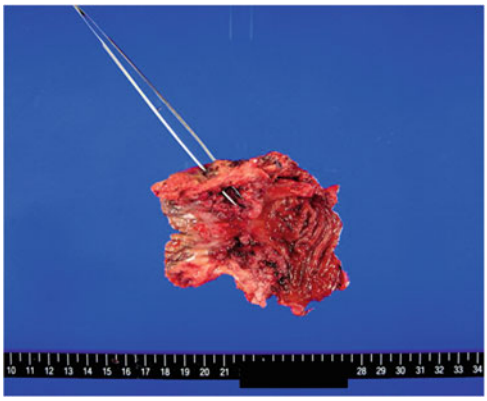

Fig. 7.7 Carcinoma in a rectovaginal fistula in a patient with CD

dysplasia or rectal dysplasia, the need for an aggressive approach, namely, TPC, is easily justified. Moreover, in CD patients with severe perianal disease or incontinence, TPC with end ileostomy offers treatment of the anal disability not provided by lesser resections such as segmental colectomy or IRA. Most surgeons favor TPC when cancer or dysplasia is discovered in the colon, but this usually results in a permanent ileostomy. Both total colectomy with ileorectal anastomosis (IRA) and segmental colectomy in CD patients with comorbidities are possible alternatives but require careful preoperative patient counseling regarding cancer risk and compulsive postoperative surveillance of any remaining colorectum.

There has been a case of colonic high-grade dysplasia (HGD) reported in a patient with CD that recurred as metastatic cancer despite subtotal colectomy followed by annual colonoscopy surveillance with biopsy [34]. Therefore, to make a definitive recommendation about the management of colonic dysplasia in CD, a large study would be required.

7.6.3 Cancer in Enteroenteric or Enterocutaneous Fistula

7.6.3.1 Characteristic

Cancer of the internal or external fistula occurring in combination with CD is not as common as cancer of the large intestine. In addition, it is very difficult to detect the disease at an early stage. This is because X-ray images of fistula cancer are similar to the images of usual CD patients.

The association between cancer and fistula has long been recognized [35–38]. Unfortunately such cancers are often unresectable. However, it is possible on occasion to carry out a radical "en bloc" resection including the fistula.

7.6.3.2 Case Presentation (Internal Fistula)

An ileal bladder fistula was found at around the age of 40 years old in a male patient, and surgical treatment was recommended. However, it was left untreated, as no symptomatic aggravation occurred. After hematuria continued for 1 month, he visited the urology department at the age of 54. A cystoscopic examination found a tumor, which was diagnosed as mucinous cancer based on biopsy findings. Total pelvic exenteration was performed. A perioperative radiogram image and the excised specimen are shown in Fig. 7.8. The patient died of cancer at 8 months after the operation.

7.6.3.3 Case Presentation (External Fistula)

An external fistulation was found between the descending colon and the skin in a 32-year-old woman, who was later referred to our hospital for surgery, as the fistula

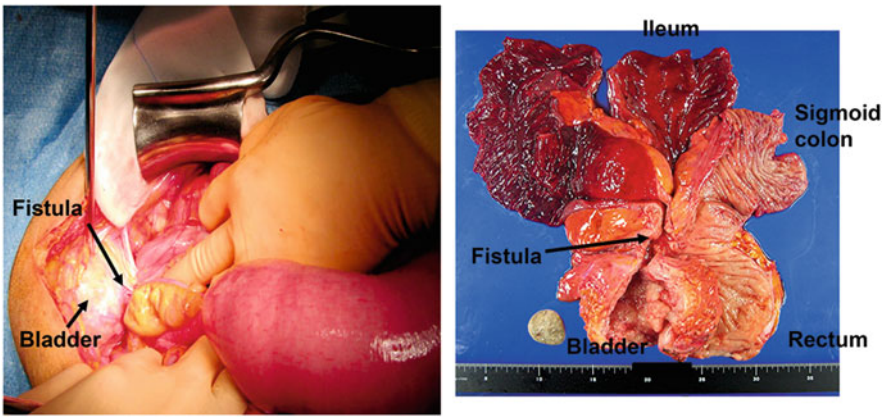

Fig. 7.8 Carcinoma between the ileum, sigmoid colon, and bladder in a patient with CD

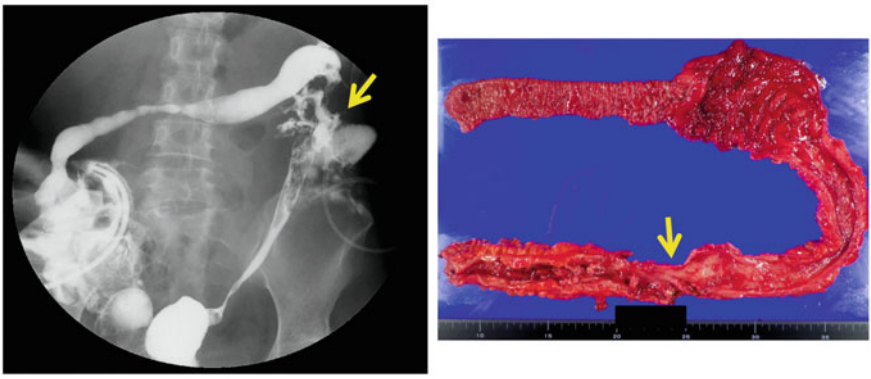

Fig. 7.9 Carcinoma between the descending colon and skin fistula in a patient with CD

did not close in spite of infliximab administration. Complete removal of the colon including 20 cm of the terminal ileum and an ileorectal anastomosis were performed. Preoperative contrast study and the excised specimen are shown in Fig. 7.9. In this case, cancer complication was demonstrated by a postoperative pathological examination of the specimen.

7.6.4 Anorectal Cancer

7.6.4.1 Characteristic

Severe chronic complicated perianal disease in patients who have CD seems to be associated with an increased risk for cancer in the lower rectum and anal canal.

Carcinoma arising in a chronic anorectal fistula in CD is rare, but the association has been reported in the literature. In most cases, it concerns a colloid carcinoma [25]. Probably chronic irritation at either end of a fistula can trigger the degeneration of scar tissue into cancer. The diagnosis is difficult, due to lack of specificity of symptoms and signs, and is often delayed, resulting in poor prognosis.

When considering prognosis, the degree of differentiation also known as the grade of the tumor is as important as the stage. Patients with well-differentiated tumors have a better prognosis and are less likely to require chemotherapy than those with poorly differentiated lesions. In CD, anal cancers more often are adenocarcinoma than squamous-cell carcinoma. Devon et al. reported that 14 of 3 patients had squamous-cell carcinomas, and the remainder had adenocarcinoma. Seven of the adenocarcinomas were well differentiated or moderately differentiated, and eight were of colloid or mucinous subtypes.

Mucinous adenocarcinoma usually occurs in about 10 % in sporadic colorectal cancer, but in cancer associated with CD, about 50 % have this more aggressive type of colorectal cancer [39].

On the other hand, Lee et al. reported that mucinous adenocarcinoma in a long-standing fistula in ano is known to be a slow-growing, locally aggressive neoplasm with a low-grade histologic appearance and rarity of metastasis. Tumor spread is usually lymphatic, and the inguinal lymph nodes are the most frequent sites of metastasis [40].

7.6.4.2 Operative Strategy

Treatment of rectal and anal cancer associated with CD involves proctectomy in the great majority of patients. In addition the colon should be resected or totally removed depending on the extension of the inflammation [41]. Treatment can be curative if the diagnosis is made early. The standard treatment option for these patients has been surgical. Abdominoperineal resection is the most frequently employed operation [42–44].

The mode of rectal amputation, i.e., abdominoperineal and sacroabdominal, is based on repositioning for the surgical approach. Ishigami et al. reported that intraoperative repositioning for patients undergoing rectal amputation helps reduce blood loss and operating time [45].

7.6.4.3 Case Presentation

Cancer that develops from a fistula around the anus is pathogenic for CD and requires extensive removal of the fistula. For surgery, sacroabdominal rectal amputation in a jackknife position is sometimes advantageous. Figure 7.10 shows a case in which an ileostomy and seton insertion were performed for aggravation of an ileal-anal lesion 10 years prior. The patient did not visit the hospital for that interim time period, as there were no symptoms, and then returned because of increased

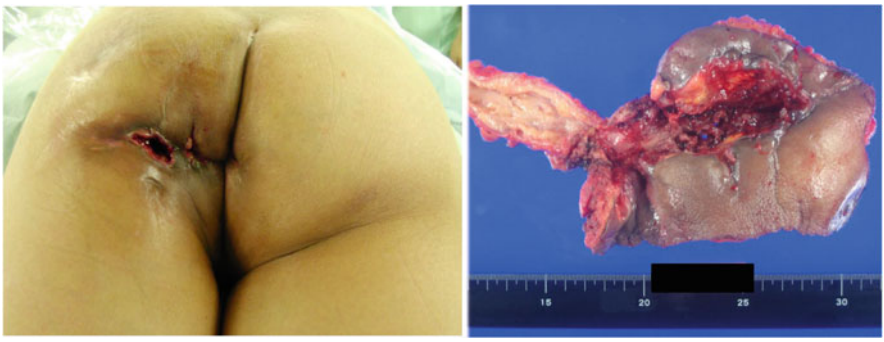

Fig. 7.10 Carcinoma in anal fistula in a patient with CD

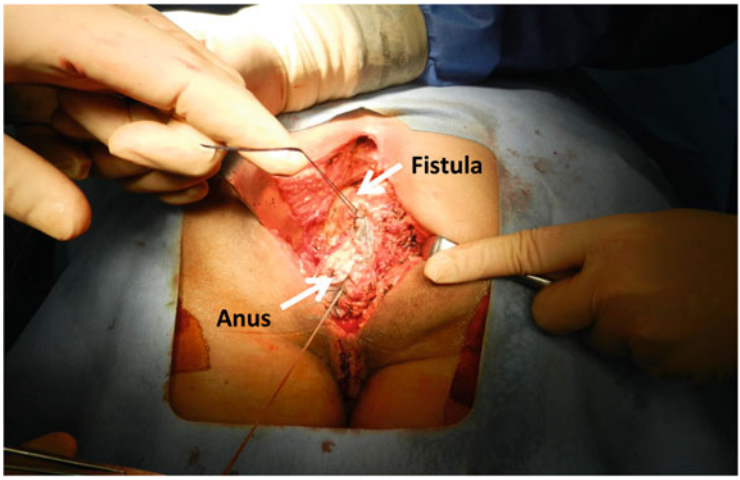

Fig. 7.11 Sacroabdominal rectal amputation

mucous excretion from the seton insertion site and pain. A pathological diagnosis of mucinous carcinoma was made. For surgery, a sacroabdominal rectal amputation was performed. Manipulation during rectal amputation on the anal side is shown in Fig. 7.11.

7.6.4.4 Pitfalls and Danger Points

Hurst reported that the abdominal perineal resection for CD entails potential pitfalls and danger points [46]. They include:

① Injury to autonomic nerves with resultant sexual and urinary dysfunction
② Ureteral injuries

③ Fecal contamination with resultant risk of intra-abdominal sepsis and wound infections
④ Improper plane of dissection along the sacrum resulting in excessive blood loss
⑤ Improper stoma placement and construction

7.6.4.5 Postoperative Complications

7.6.4.5.1 Perianal Wound Infection

Perineal wound infection often manifests with fever, perineal pain, and purulent drainage. When perineal wound infection occurs, the skin sutures are removed, and purulent fluid is completely drained. Perineal wound infection may result in a persistent perineal sinus.

7.6.4.5.2 Persistent Perineal Sinus (PPS)

Poor perineal wound healing after abdominoperineal resection for severe perianal CD was also reported by Marks et al. [47]. Persistent perineal sinus has been defined as a perineal wound that remains unhealed more than 6 months after surgery [48]. It was first reported in 1908 by Miles, as a complication of proctectomy, and it still occurs in an appreciable proportion of patients undergoing this kind of surgery [49]. Corman et al. studied 151 patients who underwent proctectomy for IBD and found poorer healing in those with CD than in those with UC [50]. In a more recent study of 427 similar patients, Bauer et al. reported primary healing in 95 % of patients with UC, but in only 67 % of those with CD [51]. Moreover, 13 % of patients with CD and only 0.8 % of those with UC had PPS after 6 months. Biopsy is recommended because chronic unhealed wounds may progress to carcinoma, especially squamous-cell carcinoma [52]. Successful management of the PPS depends on the clinical situation and the patient's condition. Conservative treatment and minor intervention, such as the application of a VAC device or curettage of the sinus, can be a feasible alternative to manage PPS.

Conservative Treatment

Conservative treatment of the sinus such as metronidazole ointment or fibrin glue can improve symptoms but often fails to achieve complete healing [52].

Vacuum-Assisted Closure

Vacuum-assisted closure (VAC) is a noninvasive, negative-pressure healing technique, which uses controlled subatmospheric pressure to remove excess wound fluid from the extravascular space, leading to improved local oxygenation and peripheral blood flow [53, 54]. There are several reports that VAC can accelerate

perineal wound healing and promote the closure of cavities, as well as increase granulation and improve the adherence of a skin graft [52].

Surgical Treatment

A wide range of surgical techniques have been described to manage perineal wound problems depending on the patient's condition and the surgeon's preference. For details, please refer to the text book.

7.6.4.5.3 Urinary Retention

Postoperative urinary retention may result from intraoperative autonomic nerve injury. Urinary retention that resulted to autonomic nerve injury is best managed with intermittent catheterization. In most instances this is required for only a limited time as bladder function tends to recover. Long-term intermittent self-catheterization is rarely necessary [46].

7.6.4.5.4 Sexual Dysfunction

Impotence is an uncommon complication following total proctocolectomy and occurs in approximately 1–2 % of male patients [55]. Retrograde ejaculation, however, is more common and occurs in up to 5 % of males.

7.6.4.5.5 Stomal Complications

Complications related to the abdominal stoma are common and include peristomal fistula, peristomal hernia, and stricture. Up to 25 % of patients will require revision of their stoma to deal with one or more of these complications [56].

7.6.5 Palliative Procedure

When the cancer is very advanced or widely metastatic, surgical treatment may not offer any benefit to the patient. At times a palliative diverting stoma is all that may be performed or all that may be indicated.

7.6.5.1 Case Presentation

An intractable anal lesion was left untreated for a long period (Fig. 7.12). A biopsy was performed under anesthesia, which showed extensive mucinous cancer ranging

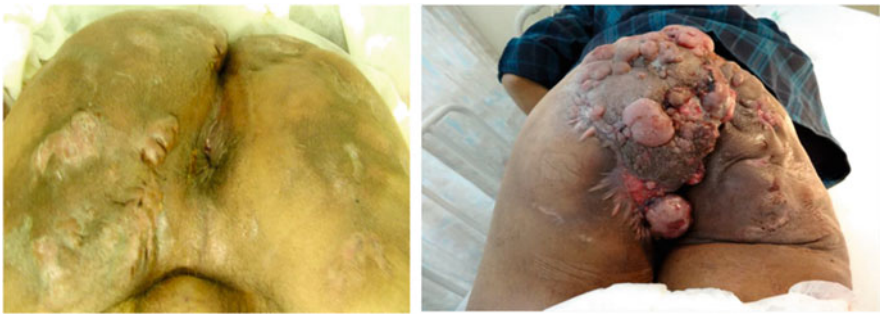

Fig. 7.12 Unresectable cancer case in a patient with CD

from around the anus to the femur, for which a radical operation was considered to be difficult (Fig. 7.12a). After a sigmoid colostomy, chemotherapy was started. The course was relatively favorable with successful local control for a period of 4 years. However, in postoperative year 5, the localized tumor became drastically enlarged and distal metastasis developed. The patient died of cancer at 5 years 10 months after surgery (Fig. 7.12b).

7.7 Postoperative Adjuvant Therapy

There is no data on the value and benefit of adjuvant therapy after curative resection of gastrointestinal cancers in CD. Recommendation for adjuvant therapy after resection of sporadic colorectal cancer can be adopted for the occasional patient with cancer complicating CD [32].

7.8 Postoperative Follow-Up

Following resection, long-term surveillance for the possibility of recurrence of the primary cancer by routine CEA or CA19-9 evaluation, as well as by CT or MRI examination when necessary, is reasonable recommendations.

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