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

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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

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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).

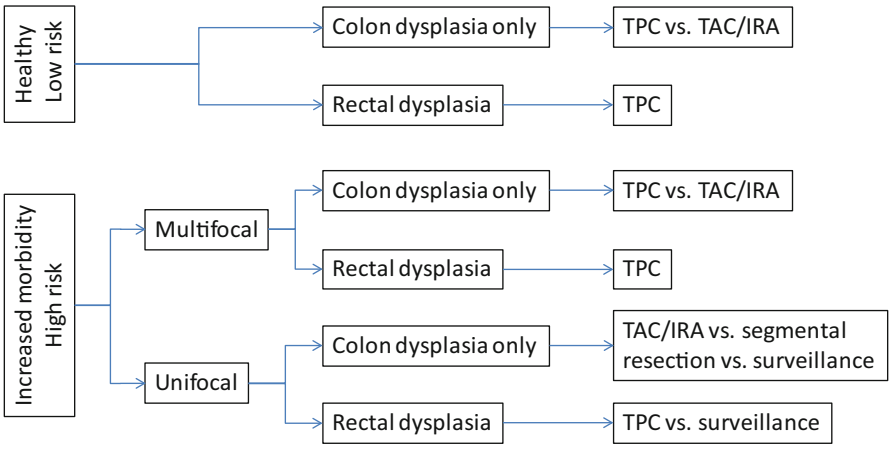

Fig. 6.1 Surgical options for ulcerative colitis patients with dysplasia found on colonoscopy. *IPAA* ileal pouch-anal anastomosis, *IRA* ileorectal anastomosis, *TAC* total abdominal colectomy, *TPC* total proctocolectomy

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]

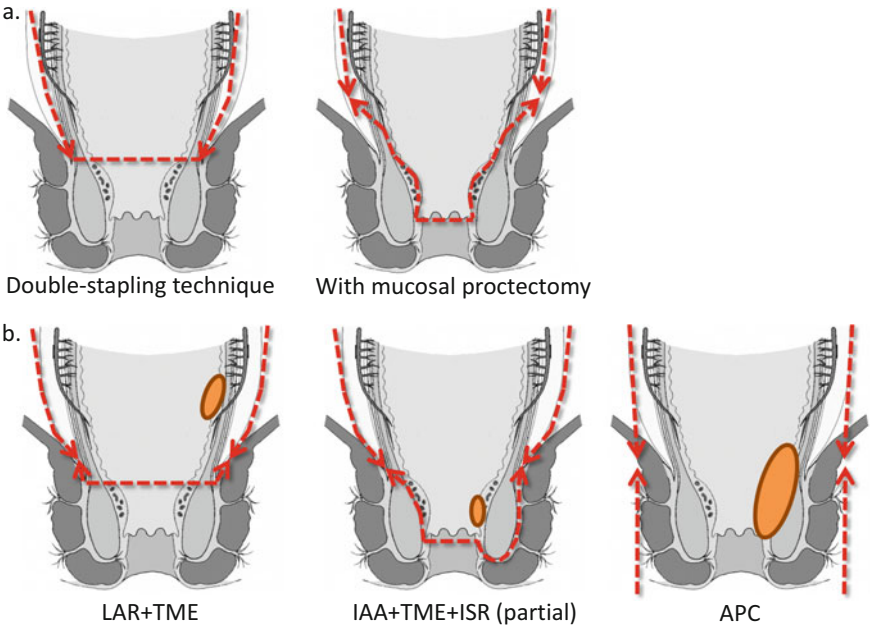

Fig. 6.2 Perianal resection line. Ileal pouch-anal anastomosis (IPAA) for ulcerative colitis (UC) (**a**), UC-associated low rectal neoplasia (**b**). *TME* total mesorectal excision, *LAR* low anterior resection, *IAA* ileoanal anastomosis, *ISR* intersphincteric resection, *APC* abdominoperineal total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

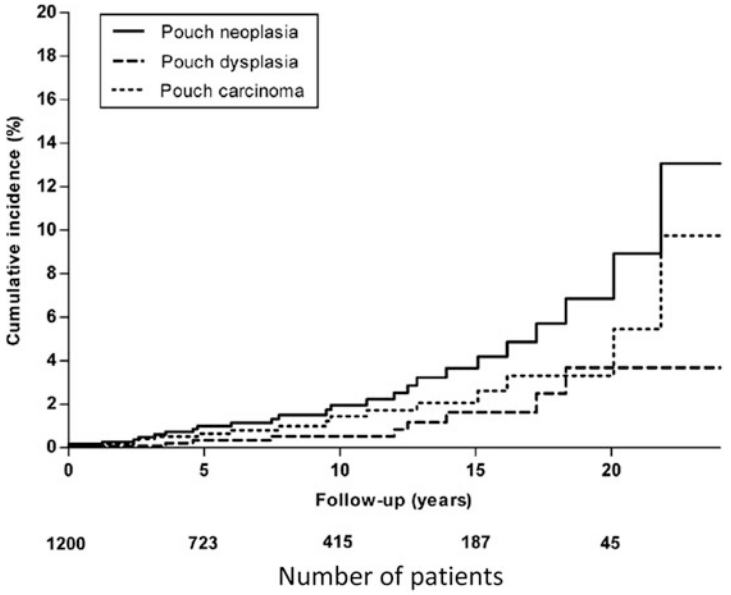

Fig. 6.3 Cumulative incidences of pouch neoplasia (both carcinoma and dysplasia), pouch carcinoma, and dysplasia (From [110])

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].

References

1. Kaplan GG et al (2012) Decreasing colectomy rates for ulcerative colitis: a population-based time trend study. Am J Gastroenterol 107(12):1879–1887
2. Mpofu C, Watson AJ, Rhodes JM (2004) Strategies for detecting colon cancer and/or dysplasia in patients with inflammatory bowel disease. Cochrane Database Syst Rev 2: CD000279
3. Eaden JA, Abrams KR, Mayberry JF (2001) The risk of colorectal cancer in ulcerative colitis: a meta-analysis. Gut 48(4):526–535
4. Ullman TA, Itzkowitz SH (2011) Intestinal inflammation and cancer. Gastroenterology 140 (6):1807–1816
5. Riddell RH et al (1983) Dysplasia in inflammatory bowel disease: standardized classification with provisional clinical applications. Hum Pathol 14(11):931–968
6. Melville DM et al (1988) Dysplasia and deoxyribonucleic acid aneuploidy in the assessment of precancerous changes in chronic ulcerative colitis. Observer variation and correlations. Gastroenterology 95(3):668–675
7. Lofberg R et al (1990) Colonoscopic surveillance in long-standing total ulcerative colitis–a 15-year follow-up study. Gastroenterology 99(4):1021–1031
8. Burmer GC et al (1992) Neoplastic progression in ulcerative colitis: histology, DNA content, and loss of a p53 allele. Gastroenterology 103(5):1602–1610
9. Leedham SJ et al (2009) Clonality, founder mutations, and field cancerization in human ulcerative colitis-associated neoplasia. Gastroenterology 136(2):542–550, e6
10. Galandiuk S et al (2012) Field cancerization in the intestinal epithelium of patients with Crohn's ileocolitis. Gastroenterology 142(4):855–864, e8
11. Lyda MH et al (2000) Microsatellite instability and K-ras mutations in patients with ulcerative colitis. Hum Pathol 31(6):665–671
12. Itzkowitz SH, Yio X (2004) Inflammation and cancer IV. Colorectal cancer in inflammatory bowel disease: the role of inflammation. Am J Physiol Gastrointest Liver Physiol 287(1):G7–G17
13. Gorfine SR et al (2000) Dysplasia complicating chronic ulcerative colitis: is immediate colectomy warranted? Dis Colon Rectum 43(11):1575–1581
14. Gumaste V, Sachar DB, Greenstein AJ (1992) Benign and malignant colorectal strictures in ulcerative colitis. Gut 33(7):938–941

15. Murphy J et al (2014) Dysplasia in ulcerative colitis as a predictor of unsuspected synchronous colorectal cancer. Dis Colon Rectum 57(8):993–998
16. Lennard-Jones JE et al (1990) Precancer and cancer in extensive ulcerative colitis: findings among 401 patients over 22 years. Gut 31(7):800–806
17. Leidenius M et al (1991) Dysplasia and carcinoma in longstanding ulcerative colitis: an endoscopic and histological surveillance programme. Gut 32(12):1521–1525
18. Nugent FW, Haggitt RC, Gilpin PA (1991) Cancer surveillance in ulcerative colitis. Gastroenterology 100(5 Pt 1):1241–1248
19. Lashner BA, Kane SV, Hanauer SB (1990) Colon cancer surveillance in chronic ulcerative colitis: historical cohort study. Am J Gastroenterol 85(9):1083–1087
20. Lynch DA et al (1993) Failure of colonoscopic surveillance in ulcerative colitis. Gut 34 (8):1075–1080
21. Lashner BA, Silverstein MD, Hanauer SB (1989) Hazard rates for dysplasia and cancer in ulcerative colitis. Results from a surveillance program. Dig Dis Sci 34(10):1536–1541
22. Bernstein CN, Shanahan F, Weinstein WM (1994) Are we telling patients the truth about surveillance colonoscopy in ulcerative colitis? Lancet 343(8889):71–74
23. Saito Y et al (1995) Total colectomy and ileorectal anastomosis in ulcerative colitis. J Gastroenterol 30(Suppl 8):131–134
24. Nugent FW et al (1979) Malignant potential of chronic ulcerative colitis. Preliminary report. Gastroenterology 76(1):1–5
25. Woolrich AJ, DaSilva MD, Korelitz BI (1992) Surveillance in the routine management of ulcerative colitis: the predictive value of low-grade dysplasia. Gastroenterology 103 (2):431–438
26. Ullman T et al (2003) Progression of flat low-grade dysplasia to advanced neoplasia in patients with ulcerative colitis. Gastroenterology 125(5):1311–1319
27. Connell WR et al (1994) Factors affecting the outcome of endoscopic surveillance for cancer in ulcerative colitis. Gastroenterology 107(4):934–944
28. Zisman TL et al (2012) Prospective study of the progression of low-grade dysplasia in ulcerative colitis using current cancer surveillance guidelines. Inflamm Bowel Dis 18 (12):2240–2246
29. Lim CH et al (2003) Ten year follow up of ulcerative colitis patients with and without low grade dysplasia. Gut 52(8):1127–1132
30. Itzkowitz SH, Harpaz N (2004) Diagnosis and management of dysplasia in patients with inflammatory bowel diseases. Gastroenterology 126(6):1634–1648
31. Kiran RP et al (2014) Risk and location of cancer in patients with preoperative colitis-associated dysplasia undergoing proctocolectomy. Ann Surg 259(2):302–309
32. Ullman TA et al (2002) The fate of low grade dysplasia in ulcerative colitis. Am J Gastroenterol 97(4):922–927
33. Kornbluth A, Sachar DB (2010) Ulcerative colitis practice guidelines in adults: American College of Gastroenterology, Practice Parameters Committee. Am J Gastroenterol 105 (3):501–523; quiz 524
34. Farraye FA et al (2010) AGA medical position statement on the diagnosis and management of colorectal neoplasia in inflammatory bowel disease. Gastroenterology 138(2):738–745
35. Farraye FA et al (2010) AGA technical review on the diagnosis and management of colorectal neoplasia in inflammatory bowel disease. Gastroenterology 138(2):746–774, 774 e1-4; quiz e12-3
36. Itzkowitz SH, Present DH (2005) Consensus conference: colorectal cancer screening and surveillance in inflammatory bowel disease. Inflamm Bowel Dis 11(3):314–321
37. Eaden JA, Mayberry JF (2002) Guidelines for screening and surveillance of asymptomatic colorectal cancer in patients with inflammatory bowel disease. Gut 51(Suppl 5):V10–V12
38. Das P et al (2007) Risk of dysplasia and adenocarcinoma following restorative proctocolectomy for ulcerative colitis. Color Dis 9(1):15–27

39. Venkatesh PG et al (2013) Natural history of low grade dysplasia in patients with primary sclerosing cholangitis and ulcerative colitis. J Crohns Colitis 7(12):968–973
40. Blackstone MO et al (1981) Dysplasia-associated lesion or mass (DALM) detected by colonoscopy in long-standing ulcerative colitis: an indication for colectomy. Gastroenterology 80(2):366–374
41. Blonski W et al (2008) High-grade dysplastic adenoma-like mass lesions are not an indication for colectomy in patients with ulcerative colitis. Scand J Gastroenterol 43(7):817–820
42. Odze RD et al (2004) Long-term follow-up after polypectomy treatment for adenoma-like dysplastic lesions in ulcerative colitis. Clin Gastroenterol Hepatol 2(7):534–541
43. Rubin PH et al (1999) Colonoscopic polypectomy in chronic colitis: conservative management after endoscopic resection of dysplastic polyps. Gastroenterology 117(6):1295–1300
44. Engelsgjerd M, Farraye FA, Odze RD (1999) Polypectomy may be adequate treatment for adenoma-like dysplastic lesions in chronic ulcerative colitis. Gastroenterology 117 (6):1288–1294; discussion 1488–91
45. Odze RD (1999) Adenomas and adenoma-like DALMs in chronic ulcerative colitis: a clinical, pathological, and molecular review. Am J Gastroenterol 94(7):1746–1750
46. Brooke BN (1961) Malignant change in ulcerative colitis. Dis Colon Rectum 4:393–398
47. Truelove SC, Witts LJ (1955) Cortisone in ulcerative colitis; final report on a therapeutic trial. Br Med J 2(4947):1041–1048
48. Lashner BA et al (1990) Dysplasia and cancer complicating strictures in ulcerative colitis. Dig Dis Sci 35(3):349–352
49. Sugita A et al (1993) Survival with colorectal cancer in ulcerative colitis. A study of 102 cases. Ann Surg 218(2):189–195
50. Varma JS et al (1987) Mucosal proctectomy and colo-anal anastomosis for distal ulcerative proctocolitis. Br J Surg 74(5):381–383
51. Schwarz RJ, Pezim ME (1991) Failure of right-sided coloanal anastomosis for treatment of left-sided ulcerative colitis. Report of a case. Dis Colon Rectum 34(7):618–621
52. Sebastian S et al (2014) Colorectal cancer in inflammatory bowel disease: results of the 3rd ECCO pathogenesis scientific workshop (I). J Crohns Colitis 8(1):5–18
53. Glickman JN, Odze RD (2008) Does rectal sparing ever occur in ulcerative colitis? Inflamm Bowel Dis 14(Suppl 2):S166–S167
54. Bousvaros A et al (2007) Differentiating ulcerative colitis from Crohn disease in children and young adults: report of a working group of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the Crohn's and Colitis Foundation of America. J Pediatr Gastroenterol Nutr 44(5):653–674
55. Rajwal SR et al (2004) Endoscopic rectal sparing in children with untreated ulcerative colitis. J Pediatr Gastroenterol Nutr 38(1):66–69
56. Robert ME et al (2004) Patterns of inflammation in mucosal biopsies of ulcerative colitis: perceived differences in pediatric populations are limited to children younger than 10 years. Am J Surg Pathol 28(2):183–189
57. Yantiss RK, Odze RD (2007) Pitfalls in the interpretation of nonneoplastic mucosal biopsies in inflammatory bowel disease. Am J Gastroenterol 102(4):890–904
58. Joo M, Odze RD (2010) Rectal sparing and skip lesions in ulcerative colitis: a comparative study of endoscopic and histologic findings in patients who underwent proctocolectomy. Am J Surg Pathol 34(5):689–696
59. Andersson P et al (2014) Ileorectal anastomosis in comparison with ileal pouch anal anastomosis in reconstructive surgery for ulcerative colitis–a single institution experience. J Crohns Colitis 8(7):582–589
60. Johnson WR et al (1986) The outcome of patients with ulcerative colitis managed by subtotal colectomy. Surg Gynecol Obstet 162(5):421–425
61. Romano G et al (1987) Role of ileorectal anastomosis in the treatment of ulcerative colitis and familial polyposis. Ital J Surg Sci 17(2):135–140

62. Oakley JR et al (1985) The fate of the rectal stump after subtotal colectomy for ulcerative colitis. Dis Colon Rectum 28(6):394–396
63. Baker WN et al (1978) Cancer of the rectum following colectomy and ileorectal anastomosis for ulcerative colitis. Br J Surg 65(12):862–868
64. Selvaggi F et al (2014) Systematic review of cuff and pouch cancer in patients with ileal pelvic pouch for ulcerative colitis. Inflamm Bowel Dis 20(7):1296–1308
65. Lutgens MW et al (2012) Risk factors for rectal stump cancer in inflammatory bowel disease. Dis Colon Rectum 55(2):191–196
66. Utsunomiya J et al (1980) Total colectomy, mucosal proctectomy, and ileoanal anastomosis. Dis Colon Rectum 23(7):459–466
67. Kim WH et al (1999) Quality of life in Korean patients with inflammatory bowel diseases: ulcerative colitis, Crohn's disease and intestinal Behcet's disease. Int J Color Dis 14(1):52–57
68. Cheung WY et al (2000) The UK IBDQ-a British version of the inflammatory bowel disease questionnaire. development and validation. J Clin Epidemiol 53(3):297–306
69. Watanabe K et al (2006) Assessment of the Japanese Inflammatory Bowel Disease Questionnaire in patients after ileal pouch anal anastomosis for ulcerative colitis. J Gastroenterol 41(7):662–667
70. Burnstein MJ et al (1987) Technique of mesenteric lengthening in ileal reservoir-anal anastomosis. Dis Colon Rectum 30(11):863–866
71. Araki T et al (2007) An alternative conversion technique for salvaging a failed ileal J-pouch-anal anastomosis to a modified H-pouch. Dig Surg 24(5):324–327
72. Kusunoki M et al (1999) Current trends in restorative proctocolectomy: introduction of an ultrasonically activated scalpel. Dis Colon Rectum 42(10):1349–1352
73. Tekkis PP et al (2005) Evaluation of the learning curve in ileal pouch-anal anastomosis surgery. Ann Surg 241(2):262–268
74. Heuschen UA et al (2002) Outcome after septic complications in J pouch procedures. Br J Surg 89(2):194–200
75. Ziv Y et al (1994) Incidence, risk factors, and treatment of dysplasia in the anal transitional zone after ileal pouch-anal anastomosis. Dis Colon Rectum 37(12):1281–1285
76. Chia CS et al (2008) Adenocarcinoma of the anal transitional zone after double stapled ileal pouch-anal anastomosis for ulcerative colitis. Color Dis 10(6):621–623
77. Al-Sukhni W et al (2010) Oncologic outcome in patients with ulcerative colitis associated with dysplasia or cancer who underwent stapled or handsewn ileal pouch-anal anastomosis. Dis Colon Rectum 53(11):1495–1500
78. O'Riordain MG et al (2000) Incidence and natural history of dysplasia of the anal transitional zone after ileal pouch-anal anastomosis: results of a five-year to ten-year follow-up. Dis Colon Rectum 43(12):1660–1665
79. Alessandroni L et al (2012) Adenocarcinoma below stapled ileoanal anastomosis after restorative proctocolectomy for ulcerative colitis. Updat Surg 64(2):149–152
80. Pedersen ME et al (2008) Adenocarcinoma arising from the rectal stump eleven years after excision of an ileal J-pouch in a patient with ulcerative colitis: report of a case. Dis Colon Rectum 51(7):1146–1148
81. Sagayama K et al (2007) Incidence of and risk factors for dysplasia in mucosectomy area in ulcerative colitis patients undergoing restorative proctocolectomy. Int J Color Dis 22 (4):439–443
82. Tsunoda A, Talbot IC, Nicholls RJ (1990) Incidence of dysplasia in the anorectal mucosa in patients having restorative proctocolectomy. Br J Surg 77(5):506–508
83. Remzi FH et al (2003) Dysplasia of the anal transitional zone after ileal pouch-anal anastomosis: results of prospective evaluation after a minimum of ten years. Dis Colon Rectum 46(1):6–13
84. Johnston D et al (1987) Preservation of the entire anal canal in conservative proctocolectomy for ulcerative colitis: a pilot study comparing end-to-end ileo-anal anastomosis without mucosal resection with mucosal proctectomy and endo-anal anastomosis. Br J Surg 74 (10):940–944

85. Galli-Gallardo SM, Pang PK, Oguro C (1979) Renal responses of the chilean toad, Calyptocephalella caudiverbera, and the mud puppy, Necturus maculosus, to mesotocin. Gen Comp Endocrinol 37(1):134–136
86. Remzi FH, Preen M (2003) Rectal cancer and ulcerative colitis: does it change the therapeutic approach? Color Dis 5(5):483–485
87. Bauer JJ et al (1997) Restorative proctocolectomy in patients older than fifty years. Dis Colon Rectum 40(5):562–565
88. Branco BC et al (2009) Adenocarcinoma complicating restorative proctocolectomy for ulcerative colitis with mucosectomy performed by Cavitron Ultrasonic Surgical Aspirator. Color Dis 11(4):428–429
89. Heimann TM et al (1984) Mucosal proctectomy using an ultrasonic scalpel. Am J Surg 147 (6):803–806
90. Monkemuller K et al (2009) Advanced colon polypectomy. Clin Gastroenterol Hepatol 7 (6):641–652
91. Vieth M, Behrens H, Stolte M (2006) Sporadic adenoma in ulcerative colitis: endoscopic resection is an adequate treatment. Gut 55(8):1151–1155
92. Rutter MD et al (2006) Thirty-year analysis of a colonoscopic surveillance program for neoplasia in ulcerative colitis. Gastroenterology 130(4):1030–1038
93. Neumann H et al (2011) Cancer risk in IBD: how to diagnose and how to manage DALM and ALM. World J Gastroenterol 17(27):3184–3191
94. Kisiel JB et al (2012) Outcome of sporadic adenomas and adenoma-like dysplasia in patients with ulcerative colitis undergoing polypectomy. Inflamm Bowel Dis 18(2):226–235
95. American Society for Gastrointestinal Endoscopy (ASGE) (1998) The role of colonoscopy in the management of patients with inflammatory bowel disease. Gastrointest Endosc 48 (6):689–690
96. Mowat C et al (2011) Guidelines for the management of inflammatory bowel disease in adults. Gut 60(5):571–607
97. Magro F et al (2013) European consensus on the histopathology of inflammatory bowel disease. J Crohns Colitis 7(10):827–851
98. Hurlstone DP et al (2007) Endoscopic mucosal resection for flat neoplasia in chronic ulcerative colitis: can we change the endoscopic management paradigm? Gut 56(6):838–846
99. Sandborn WJ, Loftus EV (2004) Balancing the risks and benefits of infliximab in the treatment of inflammatory bowel disease. Gut 53(6):780–782
100. Dixon WG et al (2010) Influence of anti-tumor necrosis factor therapy on cancer incidence in patients with rheumatoid arthritis who have had a prior malignancy: results from the British Society for Rheumatology Biologics Register. Arthritis Care Res (Hoboken) 62(6):755–763
101. Karran P, Attard N (2008) Thiopurines in current medical practice: molecular mechanisms and contributions to therapy-related cancer. Nat Rev Cancer 8(1):24–36
102. Vivarelli M et al (2008) Liver transplantation for hepatocellular carcinoma under calcineurin inhibitors: reassessment of risk factors for tumor recurrence. Ann Surg 248(5):857–862
103. Askling J et al (2011) Cancer risk with tumor necrosis factor alpha (TNF) inhibitors: meta-analysis of randomized controlled trials of adalimumab, etanercept, and infliximab using patient level data. Pharmacoepidemiol Drug Saf 20(2):119–130
104. Sigler L, Jedd FL (1969) Adenocarcinoma of the ileostomy occurring after colectomy for ulcerative colitis: report of a case. Dis Colon Rectum 12(1):45–48
105. Cuesta MA, Donner R (1976) Adenocarcinoma arising at an ileostomy site: report of a case. Cancer 37(2):949–952
106. Stryker SJ (1983) Primary stomal adenocarcinoma. An unusual complication of ileostomy. Dis Colon Rectum 26(1):47–49
107. Roberts PL et al (1989) Adenocarcinoma arising in an ileostomy. Report of two cases and review of the literature. Arch Surg 124(4):497–499
108. Cox CL et al (1997) Development of invasive adenocarcinoma in a long-standing Kock continent ileostomy: report of a case. Dis Colon Rectum 40(4):500–503

109. Nilubol N et al (2007) Mucosal dysplasia in ileal pelvic pouches after restorative proctocolectomy. Dis Colon Rectum 50(6):825–831
110. Derikx LA et al (2014) Prior colorectal neoplasia is associated with increased risk of ileoanal pouch neoplasia in patients with inflammatory bowel disease. Gastroenterology 146 (1):119–128, e1
111. Knupper N et al (2006) Adenocarcinoma of the ileoanal pouch for ulcerative colitis--a complication of severe chronic atrophic pouchitis? Int J Color Dis 21(5):478–482
112. Branco BC et al (2009) Adenocarcinoma following ileal pouch-anal anastomosis for ulcerative colitis: review of 26 cases. Inflamm Bowel Dis 15(2):295–299
113. Giebel GD, Sabiers H (1996) Ileal pouch-anal anastomosis for ulcerative colitis and polyposis coli: is the risk of carcinoma formation conclusively averted? Eur J Surg Oncol 22 (4):372–376
114. Heuschen UA et al (2001) Adenocarcinoma in the ileal pouch: late risk of cancer after restorative proctocolectomy. Int J Color Dis 16(2):126–130
115. Herfarth C, Heuschen G, Heuschen UA (1998) Malignant transformation in ulcerative colitis and surgical implications. Chirurg 69(10):1020–1027
116. Lofberg R et al (1991) Dysplasia and DNA aneuploidy in a pelvic pouch. Report of a case. Dis Colon Rectum 34(3):280–283; discussion 283–4
117. Veress B et al (1995) Long-term histomorphological surveillance of the pelvic ileal pouch: dysplasia develops in a subgroup of patients. Gastroenterology 109(4):1090–1097
118. Carey PD et al (1993) Primary adenocarcinoma in an ileostomy: a late complication of surgery for ulcerative colitis. Surgery 113(6):712–715
119. Imam MH et al (2014) Neoplasia in the ileoanal pouch following colectomy in patients with ulcerative colitis and primary sclerosing cholangitis. J Crohns Colitis 8(10):1294–1299
120. Kim BJ et al (2009) Trends of ulcerative colitis-associated colorectal cancer in Korea: A KASID study. J Gastroenterol Hepatol 24(4):667–671
121. Hughes RG et al (1978) The prognosis of carcinoma of the colon and rectum complicating ulcerative colitis. Surg Gynecol Obstet 146(1):46–48
122. Lavery IC et al (1982) Survival with carcinoma arising in mucosal ulcerative colitis. Ann Surg 195(4):508–512
123. Ritchie JK, Hawley PR, Lennard-Jones JE (1981) Prognosis of carcinoma in ulcerative colitis. Gut 22(9):752–755
124. Gorfine SR et al (2004) Restorative proctocolectomy for ulcerative colitis complicated by colorectal cancer. Dis Colon Rectum 47(8):1377–1385
125. Delaunoit T et al (2006) Colorectal cancer prognosis among patients with inflammatory bowel disease. Clin Gastroenterol Hepatol 4(3):335–342
126. Heimann TM et al (1992) Colorectal carcinoma associated with ulcerative colitis: a study of prognostic indicators. Am J Surg 164(1):13–17
127. Kavanagh DO et al (2014) Management of colorectal cancer in patients with inflammatory bowel disease. Tech Coloproctol 18(1):23–28
128. Watanabe T et al (2011) Ulcerative colitis-associated colorectal cancer shows a poorer survival than sporadic colorectal cancer: a nationwide Japanese study. Inflamm Bowel Dis 17(3):802–808
129. Jensen AB et al (2006) Survival after colorectal cancer in patients with ulcerative colitis: a nationwide population-based Danish study. Am J Gastroenterol 101(6):1283–1287
130. Larsen M et al (2007) Survival after colorectal cancer in patients with Crohn's disease: A nationwide population-based Danish follow-up study. Am J Gastroenterol 102(1):163–167
131. Shu X et al (2011) Survival in cancer patients hospitalized for inflammatory bowel disease in Sweden. Inflamm Bowel Dis 17(3):816–822
132. Inoue Y et al (2014) Chemoradiotherapy followed by restorative proctocolectomy with partial intersphincteric resection for advanced rectal cancer associated with ulcerative colitis: report of a case. Surg Today 44(2):387–390

133. Radice E et al (1998) Ileal pouch-anal anastomosis in patients with colorectal cancer: long-term functional and oncologic outcomes. Dis Colon Rectum 41(1):11–17
134. Wu XR et al (2013) Preoperative pelvic radiation increases the risk for ileal pouch failure in patients with colitis-associated colorectal cancer. J Crohns Colitis 7(10):e419–e426
135. Emami B et al (1991) Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys 21(1):109–122
136. Adenis A et al (2007) Bevacizumab and postponed suture leakages after surgery for ulcerative colitis and rectal cancer. Gut 56(5):734
137. Da Silva GM et al (2003) Histologic analysis of the irradiated anal sphincter. Dis Colon Rectum 46(11):1492–1497
138. Lorenzi B et al (2012) Short-term effects of neoadjuvant chemoradiotherapy on internal anal sphincter function: a human in vitro study. Dis Colon Rectum 55(4):465–472
139. Ito M et al (2009) Analysis of clinical factors associated with anal function after intersphincteric resection for very low rectal cancer. Dis Colon Rectum 52(1):64–70
140. Rodriguez-Enriquez S et al (2014) Canonical and new generation anticancer drugs also target energy metabolism. Arch Toxicol 88(7):1327–1350
141. Inoue Y, Kusunoki M (2010) Resection of rectal cancer: a historical review. Surg Today 40 (6):501–506
142. Inoue Y et al (2011) Push-back technique facilitates ultra-low anterior resection without nerve injury in total mesorectal excision for rectal cancer. Dig Surg 28(4):239–244
143. Kusunoki M et al (1992) Modified anoabdominal rectal resection and colonic J-pouch anal anastomosis for lower rectal carcinoma: preliminary report. Surgery 112(5):876–883