

Occult and Manifest Colorectal Carcinoma in Ulcerative Colitis: How Does It Influence Surgical Decision Making?

Julia Hardt · Peter Kienle

Department of Surgery, University Medical Center Mannheim, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany

Keywords

Ulcerative colitis · Colorectal carcinoma · Restorative proctocolectomy · J-pouch

Summary

Background: The incidence of colorectal cancer (CRC) among patients with ulcerative colitis (UC) is increased compared to the general population. The diagnosis of CRC potentially influences surgical decision making in patients with UC. **Methods:** This review considers clinical studies, systematic reviews, and guidelines on the surgical therapy of CRC in UC. We searched the bibliographic databases The Cochrane Library and Medline (applying MeSH terms such as ‘Colitis, Ulcerative/surgery’, ‘Colorectal Neoplasms’, and ‘Proctocolectomy, Restorative’) with no restriction on language, date, or country. Search results as well as references of relevant publications were independently screened by both authors of this review. **Results:** The surgical gold standard for proven CRC in UC is oncological proctocolectomy, if possible preferably as a restorative procedure with formation of an ileal pouch-anal anastomosis. Mucosectomy and hand-sewn anastomosis is the preferred option for fashioning the anastomosis in these patients, especially in case of dysplasia or cancer in the rectum, although the available data is not conclusive. In highly selected cases of patients with histologically confirmed sporadic CRC without dysplasia in multiple random biopsies and without relevant inflammation, a conventional limited oncological resection is adequate. If UC patients with rectal cancer require radiotherapy, it should be performed in a neoadjuvant setting because of the high risk of radiation-induced pouch failure. **Conclusion:** Although restorative proctocolectomy is clearly the gold standard therapy for patients with CRC in UC, surgical decision making has to take into account the various settings and patient factors.

© 2015 S. Karger GmbH, Freiburg

Introduction

The incidence of colorectal cancer (CRC) among patients with ulcerative colitis (UC) is increased compared to the general population. In a meta-analysis of 116 studies including 54,478 patients, the cumulative risk of CRC was calculated to be 2% at 10 years, 8% at 20 years, and 18% at 30 years. The overall incidence of CRC in patients with UC amounted to 3.7%, which increased to 5.4% if pancolitis was present [1]. Further disease characteristics which may carry an even higher risk of CRC are early onset of the UC, extensive mucosal involvement, long disease duration, backwash ileitis, and especially the presence of concomitant primary sclerosing cholangitis [1–4]. In the latter case the cumulative risk of cancer or dysplasia approaches 50% after 25 years. These data are in accord with recent data from North America which found the risk of CRC to be 60% higher than in the general population.

In contrast, a retrospective cohort study of more than 8,500 Hungarian UC patients reported a considerably lower cumulative risk of CRC: 0.6% at 10 years, 5.4% at 20 years, and 7.5% at 30 years [5]. A Danish cohort study including 1,160 UC patients found even lower cumulative probabilities of CRC: 0.4% at 10 years, 1.1% at 20 years, and 2.1% at 30 years. It is likely that the high colectomy rate in the Danish cohort (31% after 36 years) was the key factor of the reduced risk of CRC compared to other studies [6].

In summary, the available data on the magnitude of the documented increased risk of CRC in UC compared to the general is conflicting. In the current literature, there seems to be a trend towards a lower risk for CRC in these patients than previously thought; this possibly is the result of a more adequate medical treatment leading to a better control of chronic inflammation and hence to less development of malignancy.

On the assumption that dysplastic lesions can be detected before the development of invasive cancer the standard approach to the increased risk of cancer in patients with UC is surveillance colonoscopy. On the basis of risk factors (e.g. extent of colitis, time span from diagnosis, primary sclerosing cholangitis, etc.), guide-



Fig. 1. Ileoanal J-pouch before stapling.

lines have defined when and in which intervals patients should undergo endoscopy. Bernstein et al. [7] conducted a systematic review of ten prospective studies including 1,225 patients with UC under colonoscopic surveillance. 17 (43%) of 40 patients with dysplasia-associated lesion or mass (DALM) already had cancer at immediate colectomy. For high-grade and low-grade dysplasia the risks of synchronous cancer at immediate colectomy were 42% (10/24) and 19% (3/16), respectively [7]. However, the problem of surveillance colonoscopy is well documented by an analysis over three decades in Britain: here, 16 of 30 CRCs identified were so-called interval cancers, e.g. cancers detected after a negative index endoscopy or advanced cancers found at surveillance [8].

Although the incidence of CRC and especially the mortality due to CRC in UC patients have declined during the last two decades [5, 9, 10], surgical decision making is still complex and depends on the various scenarios in which CRC is detected or becomes manifest.

This article aims at presenting the different settings and factors which influence surgical decision making when occult or manifest CRC is diagnosed in patients with UC.

Occult Colorectal Cancer in Ulcerative Colitis

Occult cancer is defined as a clinically inapparent malignancy which is incidentally discovered while the patient is examined for other reasons (or at the time of autopsy). The setting in which occult CRC is most likely detected in UC patients is surveillance colonoscopy with random biopsies. CRCs diagnosed during surveillance endoscopy have also been termed as interval CRCs [11]. High-grade dysplasia confirmed by a reference pathologist or CRC diagnosed in an asymptomatic patient are absolute indications for elective oncologic resection.

Extent of Resection in CRC in UC

Total proctocolectomy with adequate lymph node removal in all colorectal segments is generally regarded as the resection of choice [12]. The gold standard for reconstruction is restorative proctocolectomy with formation of an ileal pouch-anal anastomosis

(IPAA) (fig. 1). In case of an advanced low rectal cancer with invasion of the sphincters a restorative procedure is not indicated; proctocolectomy with cylindrical abdominoperineal resection as in sporadic advanced rectal cancer with sphincter infiltration is the surgical procedure of choice [13].

There is no doubt that UC patients with preoperatively confirmed CRC and additional dysplasia or malignancy elsewhere in the colorectum definitely need to undergo oncologic total proctocolectomy. In such cases malignancy has occurred on the basis of an inflammation-dysplasia-carcinoma sequence, and there is a very high risk of further cancer development in the near future [14]. Moreover, many patients in this setting already show additional dysplastic lesions or cancers on workup of the colectomy specimen [7]. This also holds true for patients with high-grade confirmed dysplasia, with non-adenoma-like DALM, and with adenoma-like DALM if surrounded by flat dysplasia [15]. Adenoma-like DALM may be treated by endoscopic resection alone.

The fundamental question in patients with CRC in UC is whether there is indeed a place for limited resection in selected cases, with the rationale here being that limited resection with e.g. an ileorectostomy undoubtedly results in a better function and quality of life compared to restorative proctocolectomy or proctocolectomy with end ileostomy. There is consensus that in cancers developing on the basis of inflammation in UC, limited resection is generally contraindicated.

In the rare case of a sporadic CRC in the absence of inflammatory activity, a limited classical oncological resection, such as a hemicolectomy or a rectal resection, may be justified. However, distinguishing sporadic from inflammation-induced CRC in UC is not so simple [16]. Polypoid dysplasia and cancer associated with intestinal bowel disease may display a different pattern of genotypic abnormalities (p53, β -catenin, APC, P16, 3p), which may be used for differentiation.

In highly selected cases (e.g. women desiring to have children, elderly patients, patients with metastatic disease, or in the very rare case if an IPAA is technically not feasible) with high-grade dysplasia or CRC in the proximal colon and no or just mild disease in the rectum, ileorectal anastomosis may be considered after discussing the implications with the patient. Advantages such as better functional outcomes and preserved female fecundity have to be weighed against the need for rectal surveillance and the risk for neoplastic transformation [12]. In contrast, old age does not exclude restorative proctocolectomy in CRC because pouch function can be adequate even in septuagenarians [17]. However, if patients do have moderate or severe UC requiring aggressive medical treatment (e.g. immunosuppression), limited resection should be avoided even in sporadic cancer [18]. First of all, there probably is an increased risk of negatively influencing the oncological course in such patients, especially in more advanced cancers, if an immunosuppressive treatment is necessary later in case of persisting or deteriorating colitis in the remaining colon, as is often the case after limited resection. Secondly, if the disease does get refractory to medical treatment and the remaining colorectum needs to be removed, construction of an ileoanal pouch may be technically more difficult and in rare cases even impossible.

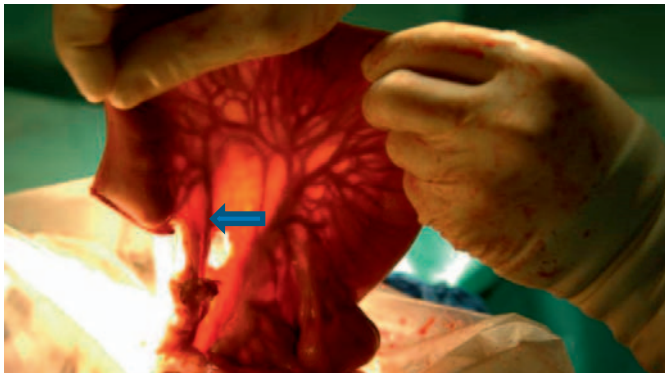


Fig. 2. Preserved ileocolic vessels in restorative proctocolectomy (arrow), allowing more lengthening options.

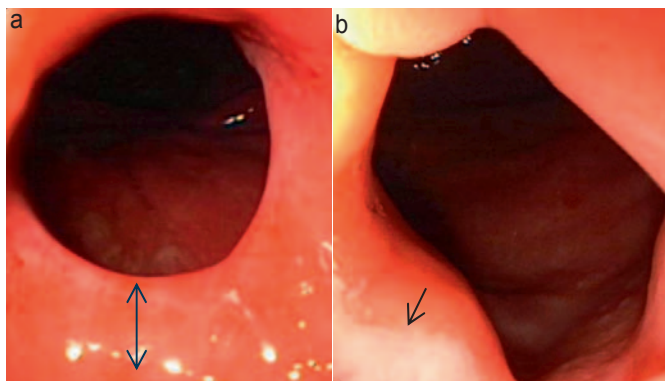


Fig. 3. **a** Stapler anastomosis in IPAA with short rectal cuff (arrow shows width of cuff) and **b** hand-sewn anastomosis in IPAA without cuff (arrow shows ileoanal anastomosis).

Technical Aspects of Surgery in CRC in UC

Patients with CRC in the colon require lymphadenectomy, which includes division of the ileocolic vessels at their origin. This reduces the options for lengthening the mesentery (fig. 2) and may result in a slightly reduced chance of successful pouch formation, especially when performing a hand-sewn pouch-anal anastomosis. In experienced centers, however, this is very rarely a problem. In very obese patients, where obtaining length can be difficult in such a scenario, an S-pouch is an option.

There is still controversy on what type of anastomosis should be done in patients with CRC in UC: stapler anastomosis with a short rectal cuff or hand-sewn IPAA (fig. 3).

At least theoretically, under oncological aspects, complete mucosectomy with hand-sewn anastomosis should be the better option as it virtually removes all colorectal mucosa, thereby potentially reducing the risk for future dysplasia and cancer in this region. There is inconclusive evidence whether mucosectomy is indeed superior to stapled anastomosis in regard to oncological outcome. A meta-analysis of 21 studies consisting of 4,183 patients who underwent IPAA compared hand-sewn versus stapled IPAA

regarding postoperative adverse events and oncological outcomes [19]. There was a statistical trend towards a higher incidence of dysplasia but not of cancer in the anal transition zone after stapled anastomosis. Further studies have confirmed that patients after stapled anastomosis have no increased cancer rate in the anorectal junction or in the pouch [20, 21]. The current German guidelines generally recommend a mucosectomy and hand-sewn anastomosis at the level of the dentate line whenever intraepithelial neoplasia or cancer is the indication for proctocolectomy [9]. In contrast, the current European Crohn's and Colitis Organization (ECCO) guidelines favor mucosectomy only when CRC or high-grade dysplasia are located in the lower rectum [12]. In all other patients both techniques can be used, bearing in mind that the meta-analysis showed better functional results after stapled anastomosis (especially in regard to nocturnal continence).

In case of rectal cancer total mesorectal excision has to be performed as radically as in sporadic rectal cancer. In case of cancer or dysplasia solely in the colon without detection of neoplastic lesions in the rectum on random biopsies, however, it seems reasonable to be a little less radical in order to better preserve the pelvic nerves and sexual function.

IPAA can be performed as a 1-, 2- or 3-stage procedure. UC patients usually undergo a 2- or 3-stage IPAA, depending very much on the general condition and the nutritional status and the medication they are on. Patients operated upon due to the disease being refractory to medical treatment or in an emergency are basically never candidates for a one-stage procedure. Though, patients treated for high-grade dysplasia or cancer often have little symptoms and in non-advanced cancers are generally in a good overall condition, thus representing potential candidates for a 1-stage approach. Nonetheless, for the majority of patients a temporary loop ileostomy is recommended because it reduces the incidence of symptomatic anastomotic leakage [12]. In our own practice we omit a protective stoma in only very selected cases (less than 2% of patients). Patients under higher-dose steroids (>10 mg Decortin) and under anti-TNF antibodies are generally no candidates for a 1-stage procedure as there is some evidence suggesting an increase in perioperative complications under such medication [22, 23].

Multimodal Treatment

Rectal cancer in UC patients is basically treated as in sporadic cancer; e.g., patients with advanced cancers and especially high-risk cancers near the mesorectal fascia should undergo neoadjuvant chemoradiation. If in doubt whether this form of treatment is really needed, it seems reasonable to indicate neoadjuvant therapy more liberally because adjuvant pelvic radiation is significantly associated with a high risk of pouch failure [24, 25]. In our own experience, virtually all patients with irradiated pouches have a severely impaired pouch function. In all patients having undergone neoadjuvant therapy a defunctioning ileostomy is strongly recommended.



Fig. 4. Second postoperative day after laparoscopic restorative proctocolectomy (2-stage procedure with protective ileostomy).

Surgical Approach: Laparoscopic versus Open

Multiple randomized controlled trials have shown that laparoscopic colectomy is as good as the open approach in CRC in regard to the oncological results [26]. The same has also been shown for rectal cancer [27]. Therefore, also in UC, CRC can be operated by minimally invasive means without oncological disadvantage for the patient, provided the learning curve of laparoscopy has been overcome. Whether the typical short-term advantages as demonstrated for other laparoscopic colorectal procedures also hold true for restorative proctocolectomy remains controversial. Feasibility and safety of the laparoscopic approach have been shown in various studies; nevertheless, clear evidence for the superiority of the laparoscopic compared to the conventional IPAA is not available. In 2009, a Cochrane review of 11 trials (of which only one was a randomized controlled trial) failed to demonstrate a difference between laparoscopic and open IPAA with regard to morbidity and mortality. However, some of the studies confirmed the most obvious advantage, i.e. a significantly improved cosmesis, if the patient had undergone laparoscopic surgery [28] (fig. 4).

Four years later, a meta-analysis of 27 studies including 2,428 patients compared adverse events and long-term function after laparoscopic versus open restorative proctocolectomy. The laparoscopic approach showed a significant association with a longer operation time, a shorter length of hospital stay, a decrease in intraoperative blood loss, and a lower incidence of wound infection. Pouch failure rates and the number of daily bowel movements did not differ between the groups. Nonetheless, laparoscopic surgery reduced the number of nocturnal bowel movements as well as pad usage during night and day significantly [29]. The LapConPouch Trial, a randomized controlled trial comparing laparoscopic versus open restorative proctocolectomy, had to be stopped prematurely

because of insufficient recruitment. Analysis of the 42 randomized patients showed equivalent postoperative outcomes in both groups except for a longer operation time and a better cosmetic result in the laparoscopic arm [30]. A retrospective analysis of data from the American College of Surgeons National Surgical Quality Improvement Program including 676 patients who underwent either open or laparoscopic IPAA found a significantly reduced rate of postoperative minor and major complications in the laparoscopic group. Nonetheless, a significant reduction in length of stay was not reached [31].

Two recent studies demonstrated significantly increased pregnancy rates after laparoscopic compared to conventional IPAA. Since laparoscopy supposedly induces less adhesion formation, tubal factor infertility usually caused by scarring and adhesions is potentially reduced [32, 33]. In our own practice around 90% of the UC patients are operated laparoscopically, principally including those with CRC, but excluding cT4 cancers on preoperative staging. Based on our experience, the cosmetic advantages of the laparoscopic approach are especially of value in the predominantly young UC patients. Moreover, patients seem to recover more quickly after the minimally invasive approach. Due to the advantages in regard to fertility, the laparoscopic approach should be the preferred method in young women who wish to conceive.

Surgical Therapy for Manifest Colorectal Cancer in Ulcerative Colitis

In more advanced stages of CRC in UC, clinical manifestation is generally no different than in patients with sporadic cancer without UC, with the classical symptoms being weight loss, abdominal pain, or change in bowel habits. Obviously, depending on inflammatory activity, these symptoms (e.g. diarrhea) may be misinterpreted though, which is one of the reasons why advanced CRC is sometimes diagnosed late in UC. In a more urgent setting with severe symptoms such as bowel obstruction, major bleeding, or perforation there is again little difference compared to non-UC patients. The clinical presentation has an impact on surgical decision making and choice of procedure. Basically, a radical oncological resection should be done whenever possible [34], in the setting of confirmed UC generally as an oncological restorative proctocolectomy. If the patient is in a deteriorated state and/or under immunosuppressive therapy, though, the type of procedure very much depends on the specific situation. In manifest ileus and bad general state, an enterostomy before the tumor in order to decompress the bowel would be the procedure of choice. After recompensation the patient should then undergo oncologic resection, preferably as restorative proctocolectomy. In cases of severe dilatation of the bowel with high risk of perforation subtotal oncological colectomy may be necessary in the emergency setting, normally as a Hartmann's procedure (3-stage procedure). If the patient is in a sepsis from bacterial translocation from the colon (e.g. beginning toxic megacolon), subtotal colectomy would again be the procedure of choice. In the case of advanced rectal cancer with an ileus or in a patient with a bad

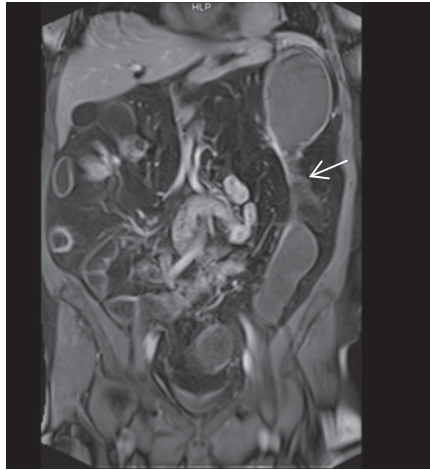


Fig. 5. MRI of a high-grade stenosis of the descending colon in UC (arrow) with pre-stenotic dilatation suspicious of malignancy.

general condition, an ileostomy or colostomy should be placed primarily in order to allow for clinical recompensation. Then, depending on the stage as in rectal cancer in non-UC patients, neoadjuvant treatment should be initiated if indicated. After completion oncologic proctocolectomy would then again be the procedure of choice.

In all decisions, the nutritional state of the patient as well as the current medications have to be considered as this may significantly influence morbidity and mortality in these patients. If the patient is in a reduced state and/or under immunosuppressive therapy, primary restorative proctocolectomy should be generally avoided.

Special Situations

Colonic Stenosis and Stricture

Colonic strictures in UC occur in up to 5% of the patients and are malignant in up to 25%. Features found to be associated with malignant colonic strictures are appearance after 20 years of duration of the disease, location proximal to the splenic flexure, and symptomatic bowel obstruction [35, 36].

Based on this evidence, the Updated German Guideline on Diagnosis and Treatment of Ulcerative Colitis and the American Society of Colon and Rectal Surgeons [15] generally recommend surgery for colonic stricture even if faced with negative endoscopic biopsy specimen [9]. The reason for this is that cancer can be missed in biopsies because of the often predominantly submucosal growth of UC-associated cancer, and secondly, the remaining colon cannot be adequately surveilled in non-traversable strictures. There is some evidence that symptomatic strictures are especially suspicious for malignancy [35] (fig. 5).

References

- 1 Eaden JA, Abrams KR, Mayberry JF: The risk of colorectal cancer in ulcerative colitis: a meta-analysis. *Gut* 2001;48:526–535.
- 2 Heuschen UA, Hinz U, Allemeyer EH, Stern J, Lucas M, Autschbach F, Herfarth C, Heuschen G: Backwash ileitis is strongly associated with colorectal carcinoma in ulcerative colitis. *Gastroenterology* 2001;120:841–847.
- 3 Soetikno RM, Lin OS, Heidenreich PA, Young HS, Blackstone MO: Increased risk of colorectal neoplasia in patients with primary sclerosing cholangitis and ulcerative colitis: a meta-analysis. *Gastrointest Endosc* 2002;56:48–54.
- 4 Velayos FS, Loftus EV Jr, Jess T, Harmsen WS, Bida J, Zinsmeister AR, Tremaine WJ, Sandborn WJ: Predictive and protective factors associated with colorectal cancer in ulcerative colitis: a case-control study. *Gastroenterology* 2006;130:1941–1949.

For colonic strictures the procedure of choice is oncological resection, preferably as an oncological restorative proctocolectomy. Only in very selected cases, where there has never been any evidence of dysplasia on random biopsies in the past, a segmental resection with intraoperative section may be an option in our opinion.

Rectal Remnant

After the rare event of a colectomy with end ileostomy for dysplasia or cancer or after detecting previously unknown high-grade dysplasia or cancer in the colonic specimen after the first step of a planned 3-stage approach the rectal remnant needs to be oncologically resected at a later stage (within 3 months). The risk of already existing or in the future developing malignancy is significantly increased in the remnant in this constellation. If the patient refuses proctectomy with preferably pouch formation, endoscopic surveillance with short intervals is mandatory.

Conclusion

The surgical gold standard for CRC in UC is oncologic restorative proctocolectomy with formation of an IPAA. In patients with dysplasia or cancer in the rectum, mucosectomy and hand-sewn anastomosis should be preferred to stapled anastomosis, although the available data here is inconclusive. In highly selected cases of histologically confirmed sporadic CRC without dysplasia in multiple random biopsies and without relevant inflammation, a conventional limited oncological resection is adequate. If UC patients with rectal cancer require radiotherapy, it should be performed in a neoadjuvant setting because of the high risk of radiation-induced pouch failure. Patients under immunosuppressive therapy or with poor nutritional status should undergo a 3-stage procedure in order to prevent septic and pouch-related complications. A laparoscopic approach may offer a better cosmesis and increase postoperative pregnancy rates in women wishing to conceive.

The available evidence in the treatment of CRC in UC patients is moderate to low. Surgical decision making has to take the specific clinical context and individual patient factors into account.

Disclosure Statement

The authors do not have any conflicts of interest to declare.

- 5 Lakatos L, Mester G, Erdelyi Z, David G, Pandur T, Balogh M, Fischer S, Vargha P, Lakatos PL: Risk factors for ulcerative colitis-associated colorectal cancer in a Hungarian cohort of patients with ulcerative colitis: results of a population-based study. *Inflamm Bowel Dis* 2006;12:205–211.
- 6 Winther KV, Jess T, Langholz E, Munkholm P, Binder V: Long-term risk of cancer in ulcerative colitis: a population-based cohort study from Copenhagen County. *Clin Gastroenterol Hepatol* 2004;2:1088–1095.
- 7 Bernstein CN, Shanahan F, Weinstein WM: Are we telling patients the truth about surveillance colonoscopy in ulcerative colitis? *Lancet* 1994;343:71–74.
- 8 Rutter MD, Saunders BP, Wilkinson KH, Rumbles S, Schofield G, Kamm MA, Williams CB, Price AB, Talbot IC, Forbes A: Thirty-year analysis of a colonoscopic surveillance program for neoplasia in ulcerative colitis. *Gastroenterology* 2006;130:1030–1038.
- 9 Dignass A, Preiss JC, Aust DE, et al: Updated german guideline on diagnosis and treatment of ulcerative colitis, 2011 (article in German). *Z Gastroenterologie* 2011;49:1276–1341.
- 10 Soderlund S, Brandt L, Lapidus A, Karlen P, Brostrom O, Lofberg R, Ekblom A, Askling J: Decreasing time-trends of colorectal cancer in a large cohort of patients with inflammatory bowel disease. *Gastroenterology* 2009;136:1561–1567; quiz 1818–1819.
- 11 Sanduleanu S, Rutter MD: Interval colorectal cancers in inflammatory bowel disease: the grim statistics and true stories. *Gastrointest Endosc Clin N Am* 2014;24:337–348.
- 12 Oresland T, Bemelman WA, Sampietro GM, et al: European evidence based consensus on surgery for ulcerative colitis. *J Crohns Colitis* 2015;9:4–25.
- 13 Holm T, Ljung A, Haggmark T, Jurell G, Lagergren J: Extended abdominoperineal resection with gluteus maximus flap reconstruction of the pelvic floor for rectal cancer. *Br J Surg* 2007;94:232–238.
- 14 Rogler G: Chronic ulcerative colitis and colorectal cancer. *Cancer Lett* 2014;345:235–241.
- 15 Ross H, Steele SR, Varma M, Dykes S, Cima R, Buie WD, Rafferty J: Practice parameters for the surgical treatment of ulcerative colitis. *Dis Colon Rectum* 2014;57:5–22.
- 16 Sada H, Shimomura M, Hinoi T, Egi H, Kawaguchi K, Yano T, Niitsu H, Saitou Y, Sawada H, Miguchi M, Adachi T, Ohdan H: Avoiding restorative proctocolectomy for colorectal cancer in patients with ulcerative colitis based on preoperative diagnosis involving p53 immunostaining: report of a case. *World J Surg Oncol* 2015;13:123.
- 17 Ho KS, Chang CC, Baig MK, Borjesson L, Noguera JJ, Efron J, Weiss EG, Sands D, Vernava AM 3rd, Wexner SD: Ileal pouch anal anastomosis for ulcerative colitis is feasible for septuagenarians. *Colorectal Dis* 2006;8:235–238.
- 18 Uchino M, Ikeuchi H, Matsuoka H, Bando T, Hirata A, Yasukawa S, Takesue Y, Tomita N: Surgical procedure for sporadic colorectal cancer in patients with mild ulcerative colitis. *Case Rep Gastroenterol* 2012;6:635–642.
- 19 Lovegrove RE, Constantinides VA, Heriot AG, Athanasiou T, Darzi A, Remzi FH, Nicholls RJ, Fazio VW, Tekkis PP: A comparison of hand-sewn versus stapled ileal pouch anal anastomosis (IPAA) following proctocolectomy: a meta-analysis of 4183 patients. *Ann Surg* 2006;244:18–26.
- 20 Al-Sukhni W, McLeod RS, MacRae H, O'Connor B, Huang H, Cohen Z: Oncologic outcome in patients with ulcerative colitis associated with dysplasia or cancer who underwent stapled or handsewn ileal pouch-anal anastomosis. *Dis Colon Rectum* 2010;53:1495–1500.
- 21 Scarpa M, van Koperen PJ, Ubbink DT, Hommes DW, Ten Kate FJ, Bemelman WA: Systematic review of dysplasia after restorative proctocolectomy for ulcerative colitis. *Br J Surg* 2007;94:534–545.
- 22 Ellis MC, Diggs BS, Vetto JT, Herzog DO: Trends in the surgical treatment of ulcerative colitis over time: increased mortality and centralization of care. *World J Surg* 2011;35:671–676.
- 23 Mor IJ, Vogel JD, da Luz Moreira A, Shen B, Hammel J, Remzi FH: Infliximab in ulcerative colitis is associated with an increased risk of postoperative complications after restorative proctocolectomy. *Dis Colon Rectum* 2008;51:1202–1207; discussion 1207–1210.
- 24 Remzi FH, Preen M: Rectal cancer and ulcerative colitis: does it change the therapeutic approach? *Colorectal Dis* 2003;5:483–485.
- 25 Taylor BA, Wolff BG, Dozois RR, Kelly KA, Pemberton JH, Beart RW Jr: Ileal pouch-anal anastomosis for chronic ulcerative colitis and familial polyposis coli complicated by adenocarcinoma. *Dis Colon Rectum* 1988;31:358–362.
- 26 Bonjer HJ, Hop WC, Nelson H, Sargent DJ, Lacy AM, Castells A, Guillou PJ, Thorpe H, Brown J, Delgado S, Kuhrij E, Haglind E, Pahlman L: Laparoscopically assisted vs open colectomy for colon cancer: a meta-analysis. *Arch Surg* 2007;142:298–303.
- 27 Bonjer HJ, Deijen CL, Abis GA, Cuesta MA, van der Pas MH, de Lange-de Klerk ES, Lacy AM, Bemelman WA, Andersson J, Angenete E, Rosenberg J, Fuerst A, Haglind E: A randomized trial of laparoscopic versus open surgery for rectal cancer. *New Engl J Med* 2015;372:1324–1332.
- 28 Ahmed Ali U, Keus F, Heikens JT, Bemelman WA, Berdah SV, Gooszen HG, van Laarhoven CJ: Open versus laparoscopic (assisted) ileo pouch anal anastomosis for ulcerative colitis and familial adenomatous polyposis. *Cochrane Database Syst Rev* 2009;1:CD006267.
- 29 Singh P, Bhangu A, Nicholls RJ, Tekkis P: A systematic review and meta-analysis of laparoscopic vs open restorative proctocolectomy. *Colorectal Dis* 2013;15:e340–351.
- 30 Schiessling S, Leowardi C, Kienle P, Antolovic D, Knebel P, Bruckner T, Kadmon M, Seiler CM, Buchler MW, Diener MK, Ulrich A: Laparoscopic versus conventional ileoanal pouch procedure in patients undergoing elective restorative proctocolectomy (LapCon-Pouch Trial) – a randomized controlled trial. *Langenbecks Arch Surg* 2013;398:807–816.
- 31 Fleming FJ, Francone TD, Kim MJ, Gunzler D, Messing S, Monson JR: A laparoscopic approach does reduce short-term complications in patients undergoing ileal pouch-anal anastomosis. *Dis Colon Rectum* 2011;54:176–182.
- 32 Bartels SA, D'Hoore A, Cuesta MA, Bensedrop AJ, Lucas C, Bemelman WA: Significantly increased pregnancy rates after laparoscopic restorative proctocolectomy: a cross-sectional study. *Ann Surg* 2012;256:1045–1048.
- 33 Beyer-Berjot L, Maggiori L, Birnbaum D, Lefevre JH, Berdah S, Panis Y: A total laparoscopic approach reduces the infertility rate after ileal pouch-anal anastomosis: a 2-center study. *Ann Surg* 2013;258:275–282.
- 34 Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft DK, AWMF): S3-Leitlinie Kolorektales Karzinom, Langversion 1.0. AWMF-Registrierungsnummer: 021–007OL. 2013. www.awmf.org/leitlinien/detail/ll/021-007OL.html.
- 35 Gumaste V, Sachar DB, Greenstein AJ: Benign and malignant colorectal strictures in ulcerative colitis. *Gut* 1992;33:938–941.
- 36 Reiser JR, Wayne JD, Janowitz HD, Harpaz N: Adenocarcinoma in strictures of ulcerative colitis without antecedent dysplasia by colonoscopy. *Am J Gastroenterol* 1994;89:119–122.