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Colorectal cancer in ulcerative colitis (review)

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ABSTRACT *Ulcerative colitis (UC) is an inflammatory bowel disease that mainly affects young people. Colorectal cancer (CRC) is one of the UC complications. This review considers the epidemiology, risk factors, diagnosis and screening, and drug prevention of CRC in UC. Various treatment options for dysplasia and CRC associated with UC are described. Taking into account the lack of literature to standardize colorectal cancer treatment approaches (especially rectal cancer) for UC, further studies are warranted to evaluate both oncological and functional treatment outcomes.*

KEYWORDS: *colorectal cancer, ulcerative colitis, dysplasia*

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INTRODUCTION

According to the WHO, in 2020, colorectal cancer (CRC) ranks 3rd among all registered oncological diseases after breast cancer and lung cancer, while 1,931,590 people were diagnosed with it during the year [1].

Ulcerative colitis (UC) is a chronic disease of the large intestine characterized by immune inflammation of its mucosal layer. The UC incidence ranges from 0.6 to 24.3 per 100,000 people; the prevalence reaches 505 per 100,000 people. The peak of morbidity is between 20 and 30 years of life, and the second peak of morbidity is described at the age of 60–70 years [2,3].

Chronic inflammation of the large intestine in ulcerative colitis can become a substrate for the development of dysplasia, carcinoma *in situ* and even invasive adenocarcinoma [4]. According to Triantafillidis J.K., et al., IBD-associated large intestine cancer accounts for less than 2% of the total CRC [5], and is the third most common after cancer associated with familial large intestine adenomatosis and Lynch syndrome [6].

To date, there are conflicting data on the rate of the CRC against the UC background. Perhaps these changes are related to the accumulation of experience and improvement of technical methods for the diagnosis of IBD [7]. Approaches to the treatment of UC-associated colorectal cancer are also ambiguous, in comparison with sporadic cancer, due to the peculiarities of its pathogenesis and the prevalence of inflammatory changes in the large intestine mucosa [8].

EPIDEMIOLOGY OF CRC AGAINST THE BACKGROUND OF UC

IBD-associated cancer has epidemiological, clinical and morphological differences from sporadic CRC.

The cancer site in UC can equally be both in the rectum and in the right and left colon; tumors are more likely to be synchronous and have a higher degree of histological differentiation. Mucinous carcinomas are more common in UC. Recently, there has been an increase in the detection rate of IBD-related cancer in the early stages (stages I-II), which reaches 60%. Delaunoit T., et al. associate this with an increased level of awareness about this disease, early start of screening and improved diagnosis [9].

Recent population studies have shown a reduction in the risk of CRC in IBD. So, Jess T., et al.

have shown that the risk ratio of the CRC in IBD is comparable to the general population — 1.07 (95% CI, 0.95–1.21). At the same time, correcting that the risk ratio of the CRC decreased from 1.34 (95% CI, 1.13–1.58) in 1979–1988 to 0.57 (95% CI, 0.41–0.80) in 1999–2008. The authors attribute this to an improvement in the results of anti-inflammatory therapy in IBD [4]. Similar results were obtained in the study by Rutter M., et al. from St. Mark's Hospital, who reported the results of the 30-year follow-up of patients with dysplasia and cancer on the UC background. The cumulative risk of CRC morbidity in this group was 2.5% after 20 years, 7.6% after 30 years and 10.8% after 40 years from the UC disease onset [10].

RISK FACTORS FOR CRC AGAINST THE UC BACKGROUND

The early age of the disease onset, the prevalence of inflammatory changes, duration and severity of the disease, family history of CRC and the presence of primary sclerosing cholangitis (PSC) were recognized as factors that increase the risk of CRC in patients with UC [11].

The most important risk factor is the duration of the disease, while the CRC occurs relatively rarely during the first 8 years after diagnosis [12].

In a large meta-analysis involving 116 studies and 54,478 patients, by Eaden J., et al., it was shown that the risk of UC-associated CRC is 0.3% per year. The cumulative CRC incidence in patients with UC was 2% after 10 years, 8% after 20 years and 18% after 30 years from the disease onset. The average duration from the diagnosis of UC to the development of CRC was 16.3 years [13].

Söderlund S., et al. revealed the dependence of the lesion extent (according to the Montreal classification) of colitis and the risk of CRC. Thus, the relative risk of developing CRC for all patients with UC was 2.7, while for proctitis — 1.7, and for total colitis — 5.6 [14]. At the same time, patients without severe inflammation of the large intestine are not at increased risk of CRC [15].

Inflammation in UC is a pathogenetic factor in the CRC, and the degree of inflammation activity is directly related to the risk of its development [16]. The presence of post-inflammatory polyps and strictures is also associated with an increased risk of a malignant process. At the same time, the large intestine strictures is an important marker of the disease severity.

It is noteworthy that almost 3.5% of large intestine strictures were diagnosed with dysplasia or CRC during biopsy. Predictors of the malignancy of strictures are their development after 20 years of illness, the location proximal to the splenic flexure and the clinical picture of bowel obstruction [10].

Patients with PSC have a higher risk of CRC. Thus, in patients with a 20-year history of UC with PSC, CRC was found in 33% of cases [17].

DIAGNOSIS AND SCREENING OF CRC IN UC

The aim of screening is to detect any dysplasia before the development of CRC, or cancer at an earlier stage, in order to improve outcomes, patient quality of life and survival [18].

Cochrane Review edited by Collins, P. et al. demonstrates that screening is effective in reducing mortality from CRC in UC by detecting cancer at an earlier stage [19]. Similar data were obtained in the study by Lutgens M., et al., which included 149 patients with CRC on the UC background. Thus, the 5-year survival rate in the screening group was 100%, while in the non-screening group it was 74%, and in the screening group colorectal cancer was detected at an earlier stage [20].

Most guidelines for UC emphasize that screening colonoscopy should be performed in patients with clinical remission, since active inflammation makes it difficult to detect dysplasia. According to the European Clinical Guidelines for the IBD treatment (ECCO), screening colonoscopies in patients with UC should be started 8–10 years after the onset of the disease for patients with left-sided or total colitis [21]. According to the Russian national clinical guidelines, screening should begin in 6–8 years [2].

The American Cancer Society (ACS) recommends screening colonoscopy in 8 years after the onset of total colitis and in 12–15 years after the onset of left-sided colitis [12].

Traditionally, screening programs recommend endoscopy in white light (WLE) with random four biopsies every 10 cm of the large intestine to detect dysplasia, which results in about 33 biopsies [2,21]. However, with a random biopsy, less than 1% of the total area of the large intestine mucosa

is examined, and the incidence of detection of dysplasia is < 2 per 1,000 biopsies [22].

The use of high-resolution endoscopic equipment leads to better visualization of the mucosal layer, which significantly increases the diagnostic value when dysplasia is detected against the UC background.

A retrospective study by Pulusu S., et al. with participation of 357 patients with IBD, has shown that high-resolution colonoscopy revealed twice as many dysplastic lesions compared to standard WLE. Moreover, it was demonstrated that dysplasia detected by random biopsy during WLE was detected in 90%-94% of cases when using high-resolution endoscopic equipment [23].

Currently, the focus is on targeted biopsies performed using chromoendoscopy (CE), or other new endoscopic methods, such as endoscopy with narrow-beam imaging (NBI) technology [22]. The sensitivity of CE in the detection of dysplasia reaches 97%, and the specificity is 93%. A prospective randomized trial by Kiesslich, R. and coauthors demonstrated the superiority of CE using methylene blue over the random biopsy technique in WLE [24].

DYSPLASIA IN UC

Most cases of CRC on the UC background develop from dysplastic lesions which can be polypoid, flat, localized or multifocal. Dysplasia is defined as a neoplastic change in the intestinal epithelium which remains confined to the basal membrane without invasion into its own plate [25].

In 1983, Riddell R., et al. developed a classification of dysplasia in IBD, which still remains relevant and includes four main categories: absence of dysplasia, indefinite dysplasia, low-grade dysplasia (LGD) and high-grade dysplasia (HGD) [26].

The pathogenesis of CRC in IBD can follow a standard path of development from the absence of dysplasia to LGD and HGD and, ultimately, lead to large intestine cancer. And also, it can develop from any dysplastic lesion (indefinite, LGD or HGD), without following the standard path. According to Navaneethan U., et al., the rate of progression of LGD to HGD or CRC over 3 years was 4.9%.

At the same time, the risk of malignant transformation is higher in flat dysplasia and dysplasia located in the distal parts of the large intestine [27]. The most important predictor for HGD and CRC from LGD is the non-polypoid (not raised above the mucosal surface). Other predictors are macroscopically invisible dysplasia, lesion size > 1 cm, and previously identified indefinite dysplasia. The greater the number of these prognostic factors, the higher the risk of LGD transformation into HGD or CRC [28].

In the presence of visible foci of dysplasia in the large intestine segments, without endoscopic signs of active inflammation, standard polypectomy should be resorted to, and further monitoring should be continued depending on the individual risk [2,12].

For visible foci of dysplasia located in polypoid lesions, endoscopic mucosal resection (EMR) is possible, but only if complete removal is achievable [29]. Currently, the standard of endoscopic resection includes taking additional biopsies from the flat mucosal layer around the site of polypectomy in order to exclude dysplasia in the surrounding tissues [30].

Follow-up of patients with fully resected dysplastic polypoid lesion depends on the lesiontype.

If there is visible dysplasia in the polypoid lesion, careful control with colonoscopy is recommended after 6–12 months. Patients with large, broad-based lesions removed by EMR or non-radical resection should repeat colonoscopy after 3–6 months, followed by annual monitoring, if initial observation revealed no signs of residual polyp growth [31]. In cases where the lesion is not subject to endoscopic resection, or there is evidence of endoscopically invisible multifocal dysplasia of low grade, or invisible dysplasia of high grade, total proctocolectomy (PCE) should be recommended [30].

Non-polypoid visible lesions should be evaluated for the safety and effectiveness of endoscopic resection [12]. In the case of endoscopic resection, a biopsy should be taken near the removal site and endoscopic tattooing should be performed in this area to facilitate future observation [32].

According to the SCENIC study, it is recommended to perform a control colonoscopy in 3–6 months after resection of non-polypoid dysplastic lesions [31]. In the case when non-polypoid formations with confirmed dysplasia cannot be removed endoscopically, the possibility of performing PCE

regardless of the dysplasia grade should be considered [12,33].

Endoscopically invisible dysplasia detected by random biopsies should be confirmed by a second independent pathologist with experience in the IBD diagnosis [2,21,34,35].

Invisible dysplasia is associated with the presence of synchronous CRC. In fact, synchronous CRC is diagnosed in 22% of patients with invisible LGD, while the CRC rate with invisible HGD ranges from 45% to 67% [10].

It is recommended to refer such patients to reference centers that treat patients with IBD and have the ability to perform high-resolution chromoendoscopy and endoscopy with repeated biopsies [31]. If dysplastic lesions are detected during chromoendoscopy, then it should be recommended to perform PCE.

In a study by Ullman, T. et al., it was demonstrated that 15.2% of patients observed with LGD developed CRC, while 23.5% of patients who underwent colectomy for LGD were also found to have HGD or CRC during histological examination [36].

This condition is an indication for performing a proctocolectomy due to the high risk of developing CRC or the presence of a synchronous lesion. According to a number of studies, when HGD was detected, a connection with synchronous CRC was revealed in 25%-67% of cases [10,36,37]. Thus, HGD is an absolute indication for PCE in most clinical guidelines [33].

To date, there is insufficient data to assess the risks and benefits of PCE with LGD in non-elevated lesions. The decision to remove the large intestine or continue follow-up should be made individually for each patient after discussion. At the same time, if the approachis chosen in favor of screening, the incidence of colonoscopy should be at least 1 time per year [2,38].

TREATMENT OF CRC IN UC

Treatment of colorectal adenocarcinoma in UC is largely based on the same principles as sporadic adenocarcinoma, with one exception — in these patients, removal of the entire colon and rectum is needed. In some cases, it is possible to restore anal defecation by J-pouch [2,39,40]. The main reason for these recommendations is the high risk of metachronous (and latent synchronous) cancer due to the UC lesion of the mucosal layer of the entire large intestine [8]. In recent reports, a number of patients have been offered more adapted treatment, including segmental resection or subtotal colectomy. In particular, the authors emphasize the importance of the specific features of the patient and the disease, such as the duration of the anamnesis, the prevalence of inflammation, clinical and endoscopic activity, the results of the biopsy and the patient's age, the state of health and his personal priorities [41,42]. In any case, the decision on the surgeryscope should be made with a consultation by coloproctologist, oncologist, gastroenterologist, and endoscopist and be discussed together with the patient.

So, the study by Khan, N. et al., included 59 patients with CRC in UC, who underwent surgery. Segmental resections were performed in 40.7%, such as low anterior rectal resection, sigmoid resection, left-sided and right-sided hemicolectomy, as well as subtotal colectomy [42]. Patients in the segmental resection group were significantly older and had less severity and prevalence of large intestine inflammation.

None of those patients developed metachronous CRC at a median follow-up of 7 years, and the results of overall survival were comparable with the results of patients from the PCE group.

In patients with a preoperative diagnosis of dysplasia or CRC, proctocolectomy should be performed according to oncological principles with high vascular ligation. Restoration of anal defecation with J-pouchis possible for most patients, whereas abdomino-perineal excision or intersphincter resection with end ileostomy should be performed in patients with low rectal cancer, in whom it is impossible to achieve adequate distal clearance, or who have anal incontinence [37].

In case of rectal cancer (RC) in ulcerative colitis, it is mandatory to conduct a multidisciplinary consultation, taking into account many available treatment options, in order to achieve optimal oncological and functional results. In addition, it was found that patients with UC have an increased risk of mortality from rectal cancer — 3.69 (95% CI, 1.66–8.22), while for colon cancer this indicator is comparable to the general population, which emphasizes need for improving the results of treatment of this particular group of patients

[44]. Treatment of RC includes radiation therapy, chemotherapy, their combination (both neoadjuvant and adjuvant), and various procedures (taking into account the radicality and functional state) [8].

In general, total mesorectumectomy (TME) is the standard treatment for early rectal cancer, while neoadjuvant chemoradiotherapy is recommended for cancers with an invasion depth greater than T2 or with lesions of regional lymph nodes [45].

In some patients, as an intermediate stage before J-pouch, colectomy with the ileo-rectal anastomosis (IRA) can be considered as a method of choice. Most often, this surgery is offered to young females who have not given birth and have no signs of inflammation or dysplasia in the rectum, in order to reduce the risk of infertility [21,43].

In cases where total proctocolectomy is performed, the only possible option to avoid permanent ileostomy and preservation of anal defecation is J-pouch [46].

Currently, the national clinical guidelines of the Russian Association of Gastroenterology and the Russian Association of Coloproctology for the diagnosis and treatment of ulcerative colitis do not recommend J-pouch in patients with rectal cancer in UC [2]. However, a number of researchers continue to look for the possibility of preserving anal defecation in this group of patients.

So, in the study by Remzi F., et al., 26 patients with RC on the UC background who underwent PCE with J-pouch are presented [47]. At the same time, the mean distance from the edge of the anal canal to the distal border of the tumor was not presented. With a follow-up period of up to 17 years, satisfactory functional results were obtained in most patients, with two deaths with the RC progression.

Thus, the authors argue that patients with RC in UC may be susceptible to TME with J-pouch if oncological principles are followed.

Merchea A., et al. described the results of treatment of 41 patients with RC on the UC background [48]. In most cases, the tumor was diagnosed at stage I or II, and was in the middle ampullary rectum. Eleven patients underwent J-pouch, while none of them underwent neoadjuvant radiation therapy. After the J-pouch, one patient developed a leakage of the ilealpouch-analanastomosis, and another, who had undergone adjuvant radiation therapy, developed radiation enteritis which required the J-pouch removal.

The overall and disease-free 5-year survival rate in this group was the same and amounted to 62%. At the same time, 89% of recurrences were in patients with stages III and IV. Thus, the authors conclude that the J-pouch in early RC on the background of UC is a justified approach.

Radiation therapy (RT) is currently the standard treatment for sporadic rectal cancer with an invasion depth greater than T2 or the presence of affected regional lymph nodes, especially in the neoadjuvant mode [45,49]. Radiation therapy for rectal cancer against the UC background has the same indications as for sporadic cancer, although its administration requires consideration of additional risk factors. There is evidence of a higher risk of severe acute toxicity in patients with IBD [50,51]. The role of RT in relation to the results of the J-pouch is not clear, since the experience is limited to a small number of clinical cases. A very high incidence of pouch anastomosis leakage during adjuvant therapy has been reported due to the effect of radiation therapy on the small intestine used in its formation [48,52,53]. In addition, pouch anastomosis leakage rate is higher, even when radiation therapy is performed in a neoadjuvant mode. But, in general, if RT is planned and the possibility of J-pouch is not excluded, neoadjuvant radiation therapy should always be preferred, as indicated in the guidelines of the European Organization for the Treatment of Crohn's Disease and Ulcerative Colitis [21,39,52,53].

Low rectal cancer is defined as rectal cancer that occurs at a distance of less than 5 cm from the edge of the anal canal during rigid proctoscopy [45]. The complexity of surgical treatment of these tumors is due to the desire to preserve the anal sphincter. For tumors located in the mesorectal margin or below, an indentation of 1 cm is considered safe enough [49]. Sporadic cancer located distal than 1 cm from the dentate line, as a rule, requires abdomino-perineal excision of the rectum (APE), although in some cases it is possible to perform intersphincter resection with ultralow anastomosis. The safe clearance along the distal edge of resection of 1 cm is based on the results of studies that have shown that distal intramural spread > 1 cm occurs only in 4%-10% of cases [54].

In addition, in a later study by Guillem J., et al. it was found that the positive distal edge of resection due to intramural growth with low sporadic RC was detected only in 1.8% of cases, and amounted to < 0.95 cm [55].

While a large number of studies for sporadic RC aimed not only at improving oncological results, but also at improving functional results, the literature data on the RC treatment against the UC background remain rather scarce do not allow to standardize the approach to its treatment. In addition, it is often difficult to specify the exact rectal lesions sites in UC during endoscopy due to their growth in a flat (not elevated) mucosa.

Hotta S., et al. analyzed the results of treatment of 11 patients with very low rectal cancer in UC [56]. In 9 cases, PCE was performed with J-pouch and pouch-anal anastomosis, and in 2 cases — APE. At the same time, the authors emphasized that in 89% of 9 cases, the cancer was in a flat (not elevated) mucosal layer surrounded by chronic inflammation, which confirms the difficulties in determining the safe distal edge of resection. As a result, neither in the PCE group with J-pouch (9 patients) nor in the APE group (2 patients) did any patient receive neoadjuvant or adjuvant radiation therapy. At the same time, the authors reported 100% overall 5-year survival in both groups. Thus, reconstructive surgery with the pouch-anal anastomosis is possible with low RC with good oncological results. However, the available literature data are insufficient for a final judgment.

The presence of ultralow RC in patients with UC causes additional concerns, because compared with colo-anal anastomosis, the J-pouch with inter-sphincter resection after PCE exposes the patient to a greater risk of unsatisfactory functional results. In patients with J-pouch after PCE, the number of daily defecations ranges from 1 to 30 (7 on average), about 5% of pouches are eventually removed due to poor functional results and unsatisfactory quality of life [57]. Therefore, with ultralow RC against the UC background, due to the high risks of unsatisfactory functional results and concerns about oncological safety, J-pouch surgery is often not offered.

In the literature, only a few successful cases of RC treatment against the UC background at a distance of less than 2 cm from the dentate line have been described, in which PCE with the J-pouch formation was performed [53,56]. And despite the success of these clinical cases, we cannot recommend this method of treatment for all patients. Neoadjuvant RT makes it possible to reduce the size and depth of tumor invasion, increasing the likelihood of reconstructive surgery [58,59]. On the other hand, it can negatively affect the function of the anal sphincter, especially in combination with low anastomosis. There is evidence that collagen deposition and nerve plexus lesion occur in the irradiated sphincter [60] and, apparently, is the main factor of poor anal function [61]. It should be emphasized that for the final decision on reconstructive surgery, along with oncological safety, it is extremely important to motivate the patient and his/her willingness to adapt and rehabilitate in the postoperative period.

PROGNOSIS FOR CRC AGAINST THE UC BACKGROUND

In a meta-analysis by Reynolds, I. et al., survival data of 243,186 patients with IBD and their risk of developing CRC in comparison with general population risks were reported. As a result, the overall 5-year survival rate of patients with IBD-associated CRC did not differ from patients with sporadic CRC — OR — 1.11 (95% CI, 0.41–2.95; $p = 0.842$). However, patients with IBD had higher risks of synchronous tumors — OR — 4.4 (95% CI, 2.32–8.36; $p < 0.001$), and the risks of rectal tumors, on the contrary, are lower — OR — 0.83 (95% CI, 0.74–0.93; $p = 0.002$) [62].

Similar data were demonstrated in the study by Thicoïpé A., et al., in which the results of treatment of two groups of patients were compared: a group with IBD-associated CRC and a group with sporadic CRC. Both groups were comparable in gender, stage and localization of the tumor.

The study showed that the cancer-specific and overall survival rates were the same in the groups of patients with CRC against the UC background and patients with sporadic CRC, 71% and 69% ($p = 0.801$), and 81% and 78% ($p = 0.845$), respectively, despite the older age in the group of sporadic CRC and a high rate of primary multiple synchronous cancer in the IBD group [63].

Summing up, it can be concluded that the prognosis for CRC associated with IBD is similar to the prognosis for sporadic CRC.

CONCLUSION

In the XXI century, the CRC incidence in 30 years after the UC diagnosis decreased from 18% to 7.6%, which is most likely due to improved results of anti-inflammatory therapy in UC. However, often, when long-term clinical remission is achieved in the treatment of UC, patients neglect to undergo screening colonoscopy, as a result of which the development of epithelial dysplasia and even CRC may be missed.

The treatment of colorectal cancer developing in patients suffering from ulcerative colitis is largely based on the same principles as in sporadic cancer, with one exception — in these patients, removal of the entire colon and rectum is indicated. In some cases, it is possible to restore anal defecation by forming a pelvic small intestine pouch.

In some patients, colectomy with the formation of ileo-rectal anastomosis can be considered as a method of choice. Patients with low localization of rectal cancer, anal sphincter incontinence should undergo colectomy with abdominal-perineal extirpation or abdominal-anal resection and ileostomy formation according to Bruck. The problem of treating rectal cancer against the UC background is quite urgent due to the lack of clear algorithms and the ambiguity of literature data. The use of radiation therapy in such patients is associated with a high risk of severe toxicity and the development of a number of severe complications in the case of the J-pouch formation.

When the patient is motivated to form J-pouch, and there are indications for CRT, the latter should be used only in the neoadjuvant mode. For the final decision on reconstructive surgery, along with oncological safety, it is extremely important that the patient is ready for a long period of adaptation and rehabilitation after surgery.

AUTHORS CONTRIBUTION

Concept and design of the study: *Arsen O. Rasulov, Artur E. Kulikov*

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