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# Cancer in Crohn's disease

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**ABSTRACT** *AIM: to assess risk factors for bowel cancer associated with Crohn's disease, as well as to assess the clinical features of the combined pathologies.*

*PATIENTS AND METHODS: retrospective study included 1,478 medical records of patients with Crohn's disease in 2020–2024. Eleven patients with bowel cancer were identified.*

*RESULTS: history analysis revealed that colorectal cancer developed mainly in patients with a long history of the CD, in whom inflammatory changes in the intestine were detected at a young age, and complications of the disease were noted as well (fistulas, strictures, perianal manifestations). For CD, patients received therapy with various genetically engineered biological agents. When colorectal cancer was detected, the tumor was localized in the colon or rectum, and had the histological structure of adenocarcinoma. After treatment (neoadjuvant chemoradiation therapy, adjuvant chemotherapy, surgery), patients were followed up for 0–16 months, during this period, relapses of Crohn's disease and colorectal cancer were not detected.*

*CONCLUSION: further studies are needed to assess the risk factors for the development of bowel cancer in the presence of Crohn's disease, the characteristics of the course of Crohn's disease after diagnosed bowel cancer, and the development of approaches to the diagnosis, treatment, and prevention of such conditions.*

**KEYWORDS:** *Crohn's disease, colorectal cancer*

**CONFLICT OF INTEREST:** *the authors declare no conflict of interest*

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## INTRODUCTION

The incidence of Crohn's disease (CD) has increased from 1.0 to 6.3 per 100,000 people over the past 40 years. The implementation of genetically engineered biological therapy and targeted immunosuppressants has significantly increased the life expectancy of patients with CD and improved its quality [1]. With a long history of CD with the presence of extensive lesions in the large intestine, the risk of colorectal cancer (CRC) increases by about 2–3 times [1]. The mechanism of CRC on the background of CD is the occurrence of areas of dysplasia on the background of long-term inflammation due to molecular changes in the *APC* and *P53* genes. Until now, the issue of oncological processes in CD patients with lesions of the rectum and anal canal has rarely been highlighted, especially in the presence of perianal fistulas, as well as in the presence of lesions of the small intestine. According to few data, small bowel cancer is a rare complication of CD with an estimated prevalence of 1.15 per 1,000 patients with CD [2]. Nevertheless, patients with CD are at increased risk of small bowel cancer, their relative risk is 33.2 times higher than that observed in the general population, and their cumulative risk is 0.2% and 2.2% after 10 and 25 years of history of small bowel cancer, respectively [3,4]. Thus, the issue of cancer against the background of CD of various localization is currently becoming more relevant. The question of possible risk factors leading to the development of malignancy against the background of CD and life expectancy after diagnosis also remains open.

## PATIENTS AND METHODS

*Characteristics of the Analyzed Group*

We analyzed 1,478 medical records of patients with previously diagnosed CD between 2020 and 2024. The medical records of 11 patients were selected, who were diagnosed with large or small intestine cancer based on the results of the examination against the background of changes caused by CD.

***Statistical Analysis***

Statistical data processing was performed in RStudio (R v. 4.4.1 (R Core Team, Vienna, Austria)) using the libraries base, gtsummary, survival, survminer. All quantitative values were represented as the median, the lower and upper quartiles (Me (Q1; Q3)), as well as the range (Min–Max). The qualitative results were given in the form of absolute and relative rates (*n* (%) or *n*/N (%)). In order to assess survival, Kaplan-Meyer's curve was constructed (death was taken as the outcome; loss from observation or an extreme visit without an outcome were considered censored).

## RESULTS

The vast majority of 11 patients were men (*n* = 9). The median age of primary detection of CD was 23 years (range from 15 to 41 years). None of the patients had a history of aggravated intestinal cancer or IBD, and there were no smokers among the patients.

The duration of the CD history before the detection of bowel cancer ranged from 2 to 26 years (median — 22 years), the median age of patients at the time of detection of bowel cancer was 43 years (37–48 years).

The characteristics of the patients are presented in Table 1.

**Table 1.** *Age, gender and anamnestic characteristics of patients*

| Indicators | Patients with CD and CRC N = 11 |
|---|---|
| Gender<br>Male<br>Female | <br>(81.8%)<br>2 (18.2%) |
| Age at the time of detection of CD, years | 23 (18; 25)<br>15–41 |
| Age at the time of bowel cancer detection, years | 43 (41; 44)<br>37–48 |
| The duration of the history of CD from the time of its detection to the diagnosis of bowel cancer, years | 22 (16; 26)<br>2–26 |

During the check-up and initial diagnosis of CD, the patients were divided as follows: ileitis was detected in 1 patient, large intestine lesions — in 6 patients, and the process was common in 4 patients with lesions of the large and small intestine (ileocolitis). In patients who were initially diagnosed with CD with the extent of inflammation in the form of ileocolitis and ileitis, the same localization persisted at the time of cancer detection, and in 4 patients with initial widespread large intestine lesion, 2 ones had inflammation detected only in the rectum (proctitis). Eight patients had a complicated CD. During the observation of the patients with CD, the presence of inter-intestinal fistulas (small bowel, small and large bowel) was detected in 4 patients. However, at the time of detection of intestinal cancer, they were detected in 3 patients.

Strictures in the small and large intestine were revealed in 7 patients, both in follow-up and at the time of detection of bowel cancer. Perianal fistulas were found at the time of detection of bowel cancer in 7 patients, while in follow-up until the diagnosis time, they were detected in 8 patients.

At the same time, the tumor was always localized against the background of a previously detected inflammatory process in the intestine. The features of the CD course before the detection of bowel cancer are presented in Table 2.

The therapy received by patients for CD was analyzed. Mainly the patients had experience using anti-TNF drugs (infliximab, adalimumab, certolizumab pegol): 4 patients in each group. One patient each had experience taking vedolizumab, upadacitinib, and ustekinumab. Also, 4 patients had a history of taking azathioprine.

Due to the long course of CD, many patients underwent an agent change during the therapy. Thus, 6 patients had a history of 1 biological agent,

**Table 2.** *Characteristics of the CD localization and complications before and at the time of detection of colorectal cancer*

| Indicators | Before bowel cancer N = 11 | At the time of detection of bowel cancer N = 11 |
|---|---|---|
| The extent of the inflammation<br>Ileit<br>Colitis<br>Ileocolitis<br>Proctitis | <br>1 (9.1%)<br>6 (54.5%)<br>4 (36.4%)<br>0 | <br>1 (9.1%)<br>4 (36.4%)<br>4 (36.4%)<br>2 (18.2%) |
| Fistulas before CRC | 4 (36.4%) | 3 (27.2%) |
| Strictures before CRC | 7 (63.6%) | 7 (63.6%) |
| Perianal fistulas before CRC | 8 (72.7%) | 7 (63.6%) |

**Table 3.** *Characteristics of the CD therapy*

| Indicators | Patients with CD and CRC N = 10 |
|---|---|
| The number of drugs in the anamnesis<br>1<br>2<br>3<br>4 | <br>6 (60.0%)<br>1 (10.0%)<br>1 (10.0%)<br>2 (20.0%) |
| Infliximab | 4 (40.0%) |
| Adalimumab | 4 (40.0%) |
| Certodizumab | 4 (40.0%) |
| Vedolizumab | 1 (10.0%) |
| Ustekinumab | 1 (10.0%) |
| Upadacitinib | 1 (10.0%) |
| Azathioprine | 4 (40.0%) |
| Total time of therapy before CRC detection, years | 6 (2; 10)<br>1–19 |

1 patient each received 2 and 3 agents, and 2 patients had experience using 4 biological agents.

It is important to note that 1 of the patients in the sample had no information about taking azathioprine, GEBD, and targeted immunosuppressants (TIS), but information about the use of mesalazine-type drugs and hormones was provided.

The characteristics of the CD therapy are presented in Table 3.

According to the results of the check-up, tumors of the small intestine ($n$ = 1), colon ($n$ = 5) and rectum ($n$ = 5) were detected in patients. When assessing the size of the tumor, invasion of the intestinal wall T2 was detected in 1 case, the remaining patients were divided equally into groups with T3 and T4.When assessing the presence of lymph node metastases in 5 patients, they were not detected, in 5 patients they corresponded to N1-N2, in 1 it was not possible to assess their presence due to the fact that the surgery was diagnostic in nature.

Distant metastases were detected in 4 cases (2 patients had peritoneal carcinomatosis, 1 patient had lung metastases, and 1 patient had pelvic bone metastases). They were not detected in 5 patients, and it was not possible to assess their presence in 2 patients due to the fact that the presence of an oncological process was revealed by the results of the surgery, and in the postoperative period, the patients were observed in other medical institutions.

The characteristics of the identified tumors are presented in Table 4.

A histological analysis revealed adenocarcinoma in 9 patients, squamous cell carcinoma in 1 case, and ring-shaped cell carcinoma in 1 case.

After the malignant neoplasm was detected, the patients were consulted by oncologists, and further treatment tactics were chosen.

Neoadjuvant chemoradiotherapy (CRT) was performed in 2 patients before the surgery.

The surgery was radical in 8 patients, and diagnostic in 2 ones (due to intraoperatively detected carcinomatosis).

In the postoperative period, 7 patients underwent adjuvant chemotherapy (CT).

Information on the patient therapy is presented in Table 5.

After the diagnosis, the patients were followed up for 0–16 months, during which 2 patients had a fatal outcome (after diagnostic operations).

## DISCUSSION

The issue of detecting malignant neoplasms in patients with CD has become increasingly relevant in recent years. For the first time, a malignant neoplasm that developed against the background of CD in the form of terminal ileitis was described in 1948, and later reports of such patients were rare. The detection rate of colorectal cancer (CRC) against the background of CD has increased since the early 2000s, which may be due, on the

one hand, to constant dynamic monitoring in this group of patients and, on the other hand, to improved laboratory and instrumental diagnostic facilities [5]. This makes it possible to diagnose CRC against the background of CD in the early stages (I-II) in 58.6% of cases, and in stage IV — in 13.4% with a median overall survival of 12.5 years and 10-year survival 55.3% (47.8%-63.9%) among all patients [6].

Risk factors for CRC against the background of inflammatory bowel diseases (IBD) include the early age of onset of the disease, the presence of concomitant primary sclerosing cholangitis (PSC), male sex, smoking, a family history of CRC and the presence of pseudopolypes [1]. When trying to clarify the risk factors for CRC against the background of CD in the literature, it was possible to identify the presence of extensive areas of inflammation in the intestine, often with the presence of inflammatory strictures, in the thickness of which it is difficult to identify the area of malignancy (even with the use of highly accurate diagnostic techniques), as well as the presence of perianal fistulas for a long time, especially against the background of chronically persistent inflammation. In the process of patient follow up most patients had an extensive inflammatory process (ileocolitis and colitis were detected in 10 patients, while the disease was chronic and continuous, indicating a long-term persistent inflammatory process). This information correlates with global data, thus confirming the fact that the risk of malignancy increases against the background of prolonged non-curable inflammation.

In the presence of perianal fistulizing of CD, the risk of cancer of the rectum and anal canal is increased 11-fold relative to the general population [7,8], while its rate is low and amounts to about 0.7% among patients with perianal CD [9]. Predictors of cancer of the rectum and anal canal are considered to be persistent rectal fistulas for more than 10 years, carriage of oncogenic strains of the herpes virus and smoking, a history of organ transplantation, as well as the practice of anal coition [10]. In the analyzed group of patients, perianal fistulizing were anamnetically noted in 8 patients, while rectal cancer was eventually diagnosed in 5 patients.

**Table 4.** *Localization and characterization of the tumor according to the TNM classification*

| Indicators | Patients with CD and CRC N = 11 |
|---|---|
| Localization of the CRC | |
| Colon | 5 (45.5%) |
| Ileum | 1 (9.1%) |
| Rectum | 5 (45.5%) |
| T | |
| 2 | 1 (9.1%) |
| 3 | 5 (45.5%) |
| 4 | 5 (45.5%) |
| N | |
| 0 | 5 (45.5%) |
| 1 | 3 (27.2%) |
| 2 | 2 (18.2%) |
| x | 1 (9.1%) |
| M | |
| 0 | 5 (45.5%) |
| 1 | 4 (36.4%) |
| x | 2 (18.2%) |

**Table 5.** *Treatment of colon cancer*

| Indicators | Patients with CD and bowel cancer N = 11 |
|---|---|
| Surgery | 10 (90.9%) |
| Surgery type | |
| Diagnostic | 2/10 (20.0%) |
| Radical | 8/10 (80.0%) |
| Neoadjuvant CRT | 2/9 (22.2%) |
| Adjuvant CT | 7/9 (77.8%) |

Screening for oncogenic strains of the herpes virus was not performed in this group, but the patients were not smokers and were not recipients after organ transplantation. Thus, the contribution of these risk factors to the development of colorectal cancer in this case is questionable.

When analyzing the data obtained as a result of the study carried out, it is impossible to draw statistically reliable conclusions due to a small sample of patients. However, it is possible to trace certain trends. Thus, the vast majority of patients were men ($n$ = 9) with common forms of CD (colitis, ileocolitis), in whom the disease debuted at a young age: 23 (15–41) years, and a significant time passed before CRC was detected: 22 (2–26) years. These data correlate with global data [11].

At the same time, there is no information on the presence of CRC or IBD in close relatives, as well as smoking in the patient's anamnesis. This is due to the small number of analyzed patients.

It is noteworthy that at the time of detection of bowel cancer, 2 patients who had previously experienced an extensive inflammatory process in the large intestine showed a decrease in the extent of inflammation with its limitation to the rectum, which may have been achieved against the background of ongoing therapy. Patients who initially had inflammatory changes in the small intestine, as well as in the small and large intestine (ileocolitis), retained this extent at the time of detection of intestinal cancer. It should be noted that at the time of detection of bowel cancer, no endoscopic remission was detected in any patient, which also supports the theory that long-lasting inflammatory changes in the large and small intestine are predictors of bowel cancer. It is noteworthy that the number of patients with complications (intestinal fistulas, strictures, perianal fistulizing) did not crucially change during the follow-up period and remained at the time of detection of bowel cancer. Due to the difficulty of detecting intestinal cancer in the thickness of the inflammatory process, especially with the development of cancer in the lumen of the fistula against the background of inflammation, the presence of these changes related to risk factors for tumors against the background of CD also confirms the global understanding of their possible causes [10].

When analyzing CD therapy, we did not focus on the use of basic drugs (steroids, antibiotics, and in some cases mesalazine). This is due to the fact that long-term follow-up did not always include a history of treatment for a particular agent, as well as their effectiveness in eliminating the manifestations of each specific exacerbation. The use of azathioprine was noted in history in 4 patients, but the time of its use was not evaluated due to the irregularity of administration in some patients. When analyzing therapy with biological therapy drugs, the time of their use was not studied due to the lack of detailed information on the duration of therapy, while there was data on the total time of biological therapy. Thus, the meantime of treatment was 6 years with a range of indicators from 1 to 19 years. However, the most interesting thing in this situation is that most of the patients had the ineffectiveness of 2 or more GEBD. It is noteworthy that the use of a large number of agents was noted in patients with the shortest history of CD. To a certain extent, both the increase in the number of drugs available for use in CD and the approaches of the 'treat-to-target' concept played a role here, when the absence of endoscopic remission requires a change in the class of the agent used. When bowel cancer was detected against the background of CD, their predominant localization was in colon and rectum, while within the framework of the TNM classification it corresponded mainly to the T3-T4 stage, which was an indication for surgical treatment. At the same time, 9 out of 10 patients included in the analysis were prescribed therapy as part of the oncological consultation: 2 patients had neoadjuvant CRT, 7 patients had adjuvant CT. It is noteworthy that after the detection of bowel cancer, the basic therapy received by patients for CD was discontinued. At the same time, no information was received about the exacerbation of CD in patients who were subsequently observed in the conditions of the RNMRC of Coloproctology.

It is not possible to identify the 5-year survival rate in the group of patients, since the follow-up period is extremely short.

## CONCLUSION

Cancer against the background of CD is a situation that has ceased to be extraordinary in recent years. It most often occurs against the background of a long history of CD in patients who were diagnosed with CD at a young age. The colon and rectum are affected with the greatest incidence in CD, while at the time of detection the tumor is widespread; histologically it most often has signs of adenocarcinoma.

Further study is needed to identify risk factors for CRC against the background of CD, as well as to develop approaches to thorough screening of patients in order to detect malignant transformation at an early stage.

**AUTHORS CONTRUBUTION**

Concept and design of the study: *Sofia S. Belous, Alexei A. Ponomarenko*
Processing of the material and statistical data processing: *Sofia S. Belous, Maria A. Ignatenko*
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