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Long-term results of treatment of patients with colorectal cancer in the context of familial adenomatous polyposis

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ABSTRACT *INTRODUCTION: familial adenomatous polyposis (FAP) is an hereditary syndrome with an autosomal-dominant type of inheritance, in which patients of young age have dozens, hundreds, and sometimes thousands of adenomatous polyps in the colorectum. If left untreated, it leads to the development of colorectal cancer (CRC) by the third or fourth decade of life. The data presented in the world literature on the characteristics of CRC in the context of FAP, the course of the disease, and the prognosis are scarce and contradictory.*

AIM: to study the long-term results of treatment of patients with CRC in the context of FAP, as well as to reveal the factors affecting survival.

PATIENTS AND METHODS: the study included 280 patients who underwent surgery for adenomatous polyposis syndrome between January 2016 and July 2024. The indication for surgery was the presence of more than 100 polyps in the colorectum and/or histologically confirmed colorectal cancer in the presence of multiple (more than 20) polyps in the colorectum. The study included only those patients who underwent radical/conditionally radical surgery with complete cytoreduction. All patients underwent molecular genetic testing (MGT) for the presence of a pathogenic variant in the APC gene, and if none was found, the study was continued with whole-exome sequencing.

RESULTS: according to the results of the MGT, 224 patients were found to have a pathogenic variant in the APC gene, and were diagnosed with familial adenomatous polyposis. Ninety-two (44 females, 48 males) of the 224 patients (41.1%) were diagnosed with colorectal cancer after the pathological examination of the removed specimens. The median age of patients with CRC at the time of surgery was 38 (19–74) years. In 30 (32.6%) of the 92 patients with CRC, the malignant disease was not diagnosed during the preoperative colonoscopy. According to the results of the pathological examination, 40 (43.5%) patients had stage I of cancer, 8 (8.7%) had stage II, 30 (32.6%) had stage III, and 14 (15.2%) had stage IV. The median follow-up period was 27.8 (5–101) months. In 14 (15.2%) patients, the disease progression was diagnosed between 5 and 36 months after surgical treatment. The median disease-free survival was 24.5 months. The actuarial 5-year survival for patients with stage I-II cancer was 100%, stage III — 82.5%, stage IV — 80%. As a result of univariant and multifactorial analyses, the following factors of a negative prognosis proved their independent importance: tumor invasion T4 (HR 14,1; 95% CI 4.62–43.2; p < 0,001), regional lymph nodes status N1a (HR 4.21; 95% CI 1.39–12.8, p = 0.011) and N2b (HR 4,85, 95% CI 1.94–18.61, p = 0.007), peritoneal dissemination M1c (HR 43.8; 95% CI 11.4–168, p < 0.001), the number of malignant tumors in the colon > 1 (HR 1.47; 95% CI 1.00–2.16, p = 0.048).

CONCLUSION: the high frequency of occult polyp malignancy in FAP patients necessitates adherence to oncological principles even during prophylactic surgery in a patient with FAP. The obtained data on the clinical features and course of CRC in patients with FAP correlate with those in patients with sporadic colorectal cancer in the same age group, which may indicate the need to apply the generally accepted approaches to the treatment of oncological patients in patients with colorectal cancer in the context of familial adenomatous polyposis.

KEYWORDS: *familial adenomatous polyposis, FAP, occult polyp malignancy, colorectal cancer, survival*

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

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INTRODUCTION

According to the literature, from 2% to 5% of colorectal cancer (CRC) cases in the world are caused by hereditary tumor diseases, namely Lynch's syndrome, familial adenomatous polyposis (FAP), *MUTYH*-associated polyposis and hamartomic polyposis syndromes [1]. At the same time, the proportion of CRC on the background of FAP does not exceed 1% of all cases of malignant colorectal neoplasms [2].

Familial adenomatous polyposis is a disease with an autosomal dominant type of inheritance, in the vast majority of cases due to the presence of a pathogenic variant in the *APC* gene. FAP manifests itself by the formation of many (tens, hundreds, and sometimes thousands) adenomatous polyps in the colorectum of young patients, as well as various extra-intestinal manifestations. In the absence of treatment, by the age of 30–40, almost all patients with the classical form of FAP experience malignant degeneration of adenomas [3]. Taking into account the inevitable malignancy of polyps in patients with FAP, in the world literature and international clinical recommendations, removal of the main target organ — the colorectum — before the development of malignant neoplasms is accepted as the main treatment method [4]. Obviously, as a result, when trying to search for data on the features of the course and prognosis in patients with colorectal cancer against the background of FAP, we came across a very small number of papers devoted to this problem, and the information provided turned out to be very contradictory. So, in the recommendations of the American College of Gastroenterology, Syngal S. et al., report that the average life expectancy of patients with colorectal cancer on the background of FAP is 2.6 years after diagnosis, referring to the data from St. Mark's Hospital (London, UK), which organized the world's first Registry of patients with colorectal polyposis back in the 1950s of the 20th century [5]. On the contrary, Bertaio L. et al., comparing survival in groups of patients with sporadic CRC (2,035 patients), colorectal cancer on the background of Lynch's syndrome (144 patients) and on the background of FAP (161 patients), concluded that the 5-year survival rates did not differ significantly in the groups and amounted to 50.6%, 56.9% and 54.4%, respectively. At the same time, it was noted that about half of the patients in all groups had early stage cancer (Dukes' stages A and B) — 51%, 52.1% and 48.4%, respectively [6].

The results obtained by Japanese researchers Inoue Y. et al. look interesting in a retrospective study of the treatment outcomes of 303 patients operated on for FAP. It turned out that 172 (56.8%) patients had confirmed the presence of colorectal cancer, of whom 56 (32.6%) patients had rectal cancer. In 25 (14.5%) patients, CRC was a finding based on the results of histological examination of the removed colorectum. Also, 113 (65.7%) patients were diagnosed with CRC at an early stage (0-II), and 59 — at stage III–IV. The overall 5-year survival rate for the entire group of patients with CRC on the background of FAP was 88.8%, compared with 98.0% for those patients who did not have CRC [7].

Mirinezhad S.K. et al. provide slightly worse results when assessing the survival rate of patients with CRC against the background of FAP in the Iranian population. Despite the fact that almost half of the patients (26/51, 50.1%) were diagnosed with stage I–II CRC, one-year, five-year and ten-year survival rates were 76%, 59% and 52%, respectively. At the same time, there was a significant difference in the five-year survival rate of patients with colon cancer and rectal cancer (75% vs. 33%, $p = 0.02$) [8].

AIM

A study of the long-term results of treatment of patients with colorectal cancer on the background of FAP, as well as identification of factors affecting survival.

PATIENTS AND METHODS

The study included 280 patients operated on for adenomatous polyposis syndrome between

January 2016 and July 2024. The clinical data on 65 patients operated on before 2019 were obtained through a retrospective search in the clinic's database. The remaining 215 patients have been included in the prospective group since 2019, when the clinic started work on the Registry of Patients with hereditary forms of Colorectal Cancer. The indication for surgery was the presence of more than 100 polyps in the large intestine and/or histologically confirmed presence of colorectal cancer on the background of multiple (more than 20) colorectal polyps. The study included only those patients who underwent radical/conditionally radical surgery with complete cytoreduction. The data on patients who were verified to have cancer based on the results of a pathomorphological examination of the removed large intestine were supplemented with information on the gender, age of diagnosis of FAP and surgery, the number and location of tumors in various parts of the intestine, the stage of the disease, the nature of preoperative and postoperative treatment, the duration and time of disease progression. In addition, all patients underwent a comprehensive molecular genetic study with the study of the entire coding sequence of the *APC* gene at the first stage, including the search for major rearrangements using the MLPA method. In the absence of pathogenic variants in the *APC* gene, the study was continued by conducting full-exome sequencing to identify possible variants in other genes associated with the development of hereditary polyposis syndromes. The presence of the detected pathogenic variants was confirmed by Sanger's sequencing. Patients who were diagnosed with a different cause of the clinical picture of adenomatous polyposis syndrome with confirmation of the presence of pathogenic variants in other genes (*MUTYH, BMPR1A, SMAD4*, etc.) were excluded from the study.

Statistical Analysis

The data obtained during the study was entered into a Microsoft Excel 2019 spreadsheet. Statistical processing of the results was performed in MedCalc statistics software v.19.6.1 (MedCalcSoftware Ltd, Belgium) and RStudio (Rv. 4.4.0 (RCoreTeam, Vienna, Austria)) using the base and Gen Binom Apps libraries. The differences were considered statistically significant at $p < 0.05$. A univariate analysis of the factors influencing the recurrence and progression of CRC was performed using Pearson's χ^2 test, while the odds ratio (OR) was calculated with a 95% coincidence interval (95% CI). To assess the significance of quantitative features in predicting the probability of outcome, the method of ROC curve analysis (Receiver Operating Characteristic) was used. It was used to determine the optimal separating value of a quantitative trait, which has the best combination of sensitivity and specificity, and the cut-off point. Significant risk factors are included in the multivariate analysis in the form of a logistic regression model.

RESULTS

In the period from January 2016 to July 2024, 280 patients were operated on at the RNMRC of Coloproctology of the Ministry of Health of Russia with a clinical picture of adenomatous polyposis syndrome. According to the results of a molecular genetic study in 224 patients, the presence of a pathogenic variant in the *APC* gene was revealed, and a diagnosis of familial colorectal adenomatosis was established.

27 (9.6%) patients were found to have pathogenic variants in other genes (*MUTYH, BMPR1A, SMAD4*, etc.), as a result of which they were excluded from the study. It was impossible to determine the genetic cause of the disease in twenty-nine patients. Colorectal cancer was diagnosed in 92 (41.1%) of 224 patients with FAP based on a pathomorphological examination of the removed large intestine. The clinical and demographic characteristics of patients with CRC are shown in Table 1.

Taking into account the data on the necessarily precancerous nature of the disease, the main target of which is the colorectum, the task of surgery

Table 1. *Demographic and clinical characteristics of patients with CRC in the context of FAP*

Characteristics	N = 92	
Gender (females/males), *n*	44/48	
Age at the time of surgery, median (.), years	38 (32,44)	
Age of diagnosis of FAP, median (.), years	35 (30,42)	
Primary patients/relatives of previously treated patients, *n*	81/11	
	Endoscopy:	**Pathomorphology:**
The presence of cancer only in the colon, *n* (%)	31 (33.7%)	49 (53.2%)
The presence of cancer only in the rectum, *n* (%)	22 (24%)	25 (27.2%)
The presence of cancer in the colon and rectum, *n* (%)	9 (9.8%)	18 (19.6%)
Without colorectal cancer, *n* (%)	30 (32.6%)	–
The presence of distant metastases before surgery, *n* (%)	10 (17.6)	
Neoadjuvant treatment, *n* (%)	15 (26.8)	
The number of malignant tumors in the removed specimens, *n*	164	
The number of malignant tumors in the colon, total/median/min–max	110 / 1 / 1–6	
The number of malignant tumors in the rectum, total/median/min–max	54 / 1 / 1–3	

in all patients was to remove the latter. Thus, 82 (89%) patients underwent primary coloproctectomy, and 10 patients underwent surgery to remove the remaining parts of the large intestine after previously performed segmental resection. It should be noted that the data of the preoperative examination of patients differed slightly from the results of the pathomorphological examination of the removed specimens. Thus, in 30 (32.6%) patients, the conclusions based on the results of the main diagnostic method in FAP — endoscopy — did not contain data on malignancy and/or suspected malignancy of colorectal polyps, while the final pathomorphological analysis indicated the presence of malignant growth. In 10 patients with CRC, the presence of distant liver metastases was diagnosed at the preoperative stage, 8 of whom underwent neoadjuvant systemic chemotherapy, and all the patients subsequently underwent combined surgery with liver resection and full cytoreduction. Also, in 4 patients, as an intraoperative finding, tumor foci were found on the visceral and/or parietal peritoneum in the area of the primary colorectal tumor without visible dissemination to the other areas of the abdominal cavity — they were regarded as manifestations of local carcinomatosis and removed *en bloc* with colorectal specimen. Neoadjuvant chemoradiotherapy was performed in seven patients with cancer localized in the middle-lower ampullary rectum according to the current clinical guidelines [9].

According to the results of a pathomorphological examination of the surgical material, 40 (43.5%) patients were diagnosed with the first stage of cancer according to the UICC [10], 8 (8.7%) patients had the second stage, 30 (32.6%) had the third, and 14 (15.2%) patients had the fourth stage (Table 2).

All patients were followed up for a period of 5 to 101 months with a median follow-up of 27.8 months. In 14 (15.2%) patients, the disease progressed in the form of distant metastases in the liver, lungs, brain, and skeletal bones within 5 to 36 months after surgical treatment, and systemic chemotherapy was started for all of them. The median disease-free survival was 24.5 months. Four patients died from the dissemination of the tumor process 6–49 months after the surgery. The actuarial 5-year survival rate for patients with stage I-II cancer was 100%, stage III — 82.5%, stage IV (after surgical treatment with complete cytoreduction) — 80% (Fig. 1).

To identify factors that negatively affect the survival of patients with colorectal cancer on the background of FAP, a univariate analysis was performed, according to which statistically significant indicators were: the depth of invasion of the T4 stage tumor, criteria N1a, N1b, N2b, M1c, stages III and IV according to the UICC, as well as the number of malignant tumors in the colon. In order to identify independent factors of a negative prognosis for CRC against the background of

Table 2. *Tumor staging in patients with CRC in the context of FAP according to TNM and UICC [10]*

Staging of the tumor process	n (%)
As per criterion T	
1	31 (33.7)
2	17 (18.5)
3	25 (27.1)
4	19 (20.7)
As per criterion N	
0	48 (52.2)
1a	13 (14.1)
1b	6 (6.5)
2a	13 (14.1)
2b	12 (13.1)
As per criterion M	
0	78 (84.8)
1a	10 (10.9)
1c	4 (4.3)
The UICC stage	
I	40 (43.5)
II	8 (8.7)
III	30 (32.6)
IV	14 (15.2)

FAP, a multiple regression logistic analysis was performed, in which the results of the univariate analysis were immersed. As a result of the analysis, the following proved their importance as independent factors: the depth of tumor T4 invasion (HR 14.1; 95% CI 4.62–43.2; $p < 0.001$), N1a (HR 4.21; 95% CI 1.39–12.8, $p = 0.011$), N2b (HR 4.85, 95% CI 1.94–18.61, $p = 0.007$), M1c (HR 43.8; 95% CI 11.4–168, $p < 0.001$), the number of malignant tumors in the colon > 1 (HR 1.47; 95% CI 1.00–2.16, $p = 0.048$).

The results of the factor analysis are shown in Table 3.

DISCUSSION

The aim of our study was to identify the clinical features of colorectal cancer that occurs against the background of familial colorectal adenomatosis, as well as to determine the prognosis in this category of patients. The need for such study arose due to the contradictory results of earlier studies, as well as the small number of them [5–8, 11]. In addition, a statistical analysis was performed to identify prognostic factors affecting the survival of patients with CRC on the background of FAP.

Among the results obtained, first of all, the high percentage of malignated polyps undiagnosed at the preoperative stage in patients with FAP is noteworthy — 32.6% — despite the fact that in most cases colonoscopy was performed in a specialized center. Unfortunately, we have not found

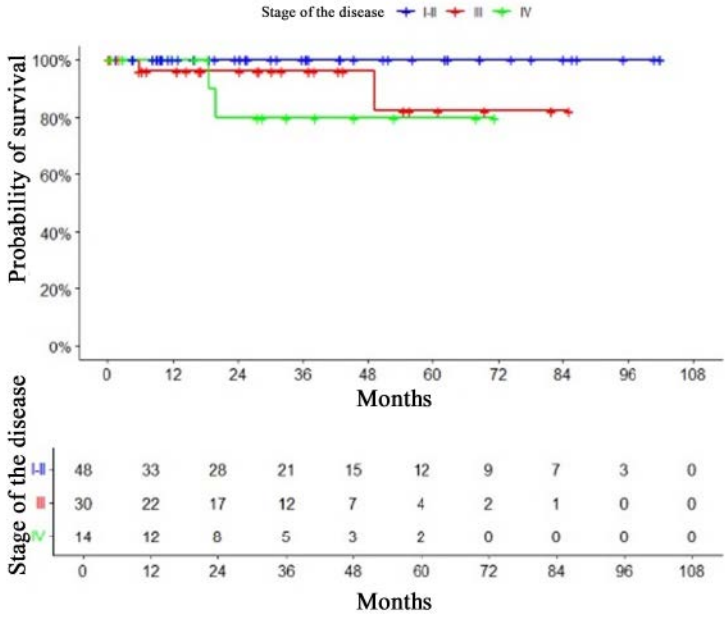

Figure 1. *Survival in patients with CRC in the context of FAP*

Table 3. *Results of univariate analysis and multiple logistic regression analysis of factors affecting the survival of patients with CRC in the context of FAP*

Indicators	Univariate analysis HR (95% CI)	*p*	Multiple Logistic Regression HR (95% CI)	*p*
Gender				
Females	–			
Males	2.04 (0.68–6.11)	0.20	–	–
Age at the time of surgery	1.00 (0.96–1.05)	0.97	–	–
T index				
1	–		–	
2	3.49 (0.32-38.5)	0.31	–	–
3	5.41 (0.56-52.1)	0.14	–	–
4	17.2 (2.10-141)	0.008	14.1 (4.62-43.2)	< 0.001
N index				
0	–		–	
1a	12.4 (2.39-64.4)	0.003	4.21 (1.39-12.8)	0.011
1b	8.24 (1.16-58.6)	0.035	1.47 (0.32–6.63)	0.62
2a	4.15 (0.58-29.5)	0.16	–	–
2b	8.89 (1.47-53.8)	0.017	4.85 (1.94-18.61)	0.007
M index				
0	–		–	
1a	3.42 (0.91-12.9)	0.070	6.21 (1.61-24.0)	0.008
1c	14.6 (3.61-59.1)	< 0.001	43.8 (11.4-168)	< 0.001
UICC stage				
I	–		–	
II	0.00 (0.0-1)	> 0.99	–	–
III	5.25 (1.05-26.1)	0.043	1.00 (0.33–3.03)	> 0.99
IV	13.2 (2.64–6.1)	0.002	1.00 (0.30–3.29)	> 0.99
n CRC in the colon > 1	1.65 (1.14–2.38)	0.008	1.47 (1.00–2.16)	0.048
n CRC in the rectum > 1	1.03 (0.53–2.01)	0.92	–	–

data in the literature on the frequency of latent malignancy in patients with FAP. However, the results obtained correlate with those identified in the study by Chernyshov S.V. et al. The diagnostic accuracy of endoscopic examination in the verification of latent adenocarcinomas in the adenomas of the rectum was only 77% with a sensitivity of 0.56 and a specificity of 0.84 [12].

In our cohort of patients, the detection rate of colorectal cancer among patients with FAP was 41.1%, which can be considered a good indicator, especially considering the fact that 81 out of 92 patients were initially treated based on clinical symptoms. A similar frequency is evidenced by earlier data from Gibbons, D.C. et al. [13] and Mallinson, E.K. et al. [14], who detected CRC in patients with FAP in the registry of St. Mark's Hospital and the Manchester Polyposis Registry in 33.6% and 43.5%, respectively. However, both studies provide data on patient samples before the start of the stage of active detection of FAP, while in the subsequent period, screening in the risk group allowed to reduce these indicators to 5.1% and 3.8%, respectively. Taking into account the early age of CRC in FAP (the median age of cancer diagnosis in our study was 38 years), literature data on young patients with sporadic colorectal cancer were selected as a comparison of clinical and morphological characteristics and prognosis of the course. So, according to Kim, T.J. et al.'s paper summarizing data on 693 patients under 45 years of age (median age — 38 years) patients with sporadic colorectal cancer were found to have a high detection rate of stage III and IV cancer — 55.6% [15]. In our study, the same indicator was slightly lower, amounting to 47.8% (44/92 patients). At the same time, 15.2% of patients had disease progression with a median follow-up of

27.8 months. Kim T.J. et al., in turn, report a recurrence rate of 23.1% of cases with a median follow-up of 66.4 months. The authors also provide data on 5-year cancer-specific survival rates of 98.5%, 93.7%, 78.2% and 39% for stages I, II, III and IV of cancer, respectively [15]. The data obtained in our study on 5-year survival also correlate with the reported results of patients with sporadic CRC. When conducting a factor analysis aimed at identifying factors affecting the survival of patients with CRC on the background of FAP, data were obtained on the depth of T4 tumor invasion, the degree of damage to regional lymph nodes N1a and N2b, the presence of peritoneal dissemination of the M1c tumor, as well as the number of malignant tumors in the colon > 1 as independent factors of a negative prognosis of the disease. At the same time, it is known that these same factors worsen the prognosis of the course and sporadic cancer. So, in the study by Gunderson L.L. et al. tumor overgrowth of the visceral peritoneum and neigh boring organs was also an unfavorable factor in survival [16]. Bertario L. et al, noted the presence of distant metastases (Dukes' stage D) as a statistically significant factor affecting survival (p = 0.002) [6]. In the study by Mirinezhad S.K. et al., according to a multivariate analysis, the presence of distant metastases was also a statistically significant factor (p = 0.001).However, the lesion of regional lymph nodes turned out to be an insignificant sign (p = 0.86), which is probably due to the small number of patients with N1 and N2 [8].

CONCLUSION

Thus, based on the conducted study, it can be concluded that the frequency of CRC detection in the cohort of patients with FAP was 36.4%. At the same time, the presence of malignant growth during colonoscopy was not detected in 32.6% of cases (in 30 out of 92 patients with CRC), which may indicate a high incidence of latent malignancy of polyps in FAP. Given the identified feature, when performing even preventive intervention in a patient with FAP, surgical treatment in compliance with oncological principles is preferable in the form of removal of the specimen in a single block with removal of regional metastasis pathways and high ligation of the main blood vessels.

The data obtained on the clinical features and course of colorectal cancer in patients with FAP correlate with those in patients with sporadic colorectal cancer in the same age group, which may indicate the need to apply generally accepted approaches to the treatment of cancer patients. It is also necessary to note the possibility of CRC prevention in patients with FAP by early detection of the disease through active screening among the high-risk group.

AUTHORS CONTRIBUTION

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Statistical processing: *Dmitriy Yu. Pikunov*

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