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Factors of Unfavorable Prognosis in Stage III Colorectal Cancer

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Abstract The study and identification of prognostic factors affecting long-term treatment results will allow individualizing the treatment of patients with stage III of the disease. The study obtained the following predictors of the prognosis of disease progression (distant metastases): the degree of tumor invasion (T4), metastatic lesion of regional lymph nodes (N2) and the absence of adjuvant chemotherapy, which showed a significant effect in multivariate analysis.

Keywords Colorectal cancer, Prognosis, Risk factors, Metastases, Chemotherapy

1. Introduction

Colorectal cancer (CRC), due to the increasing incidence, remains a serious health problem worldwide. According to Cancer Today, 1,926,425 cases of the disease and 904,019 deaths from CRC have been registered worldwide. In Asia, more than 960,000 new cases and more than 460,000 deaths were reported in 2022. In 2022, CRC ranks third in the cancer incidence structure (10.3%): among the male population after lung and prostate cancer, among the female population after breast cancer and lung cancer [1].

In the Republic of Uzbekistan, according to official statistics, 1,818 patients with colorectal cancer were identified in 2022, of which 290 patients (16.0%) were diagnosed with stage IV disease. 936 patients died from colorectal cancer in the country. The ratio of the deceased to the sick remains high, reflecting the effectiveness of anti–cancer measures, including diagnostic and therapeutic measures, in 2022 - 51.5% [2].

Surgery is the main method of treating CRC. For shallow tumors, endoscopic resection is the recommended treatment option, provided the patient is properly monitored [3]. More infiltrative tumors require surgical intervention. The purpose of resection is to remove the tumor and adjacent lymph nodes. In colon cancer, the volume of resection depends on lymphovascular drainage in the tumor area, but should cover a segment of the colon at least 5 cm long on each side of the tumor [4]. It is also important to examine and, if possible, palpate the abdominal and pelvic organs, as well as the abdominal cavity, to ensure that there are no metastases. Partial colectomy can be performed laparoscopically with preservation of the oncological outcome, but with a faster recovery after surgery compared with open surgery [5,6]. Surgical treatment of the disease is possible in patients with stage IV, but the selection of patients for resection of metastases is of great importance. The approach to patients with metastases should be multidisciplinary, while taking into account both technical and prognostic factors [7].

Surgical treatment, as an independent method, is effective for colon cancer in stages I-II. In colon cancer of the first stage of the disease, the effectiveness of surgical intervention as an independent treatment method has been proven, in other cases, it is necessary to conduct a preoperative course of radiation therapy [8]. About 25-40% of patients treated with CRC according to the radical program (stages I-II) develop a relapse of the disease or distant metastases appear. Distant metastases, among patients with stage III of the disease, appear in almost 35% of cases after potentially radical treatment. The progression of the disease, in this case, is due to the activation of tumor cells that migrated even before surgery from the primary localization of the tumor. Adjuvant chemotherapy is prescribed worldwide to solve this problem [9,10].

Thus, the increase in the incidence of CRC worldwide, including in the Republic of Uzbekistan, the high frequency of disease progression after treatment determines the relevance of this issue for the oncological service. The study and identification of prognostic factors affecting long-term treatment results will allow individualizing the treatment of patients with stage III of the disease.

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Table 1. The main characteristics of patients

Criteria	Colorectal cancer			
	in total	the colon	rectosigmoid compound	the rectum
Number of patients, %	180 (100%)	119 (66,1%)	26 (14,4%)	35 (19,4%)
Gender				
men	117 (65%)	77 (64,7%)	11 (42,3%)	29 (82,9%)
women	63 (35,0%	42 (35,3%)	15 (57,7%)	6 (17,1%)
Age, years				
Median	62,5	64,0	62,0	57,0
(lower-upper quartile)	(56,0-67,8)	(57,0-70,0)	(54,0-65,3)	(54,0-66,0)
T				
T2	7 (3,9%)	2 (1,7%)	2 (7,7%)	3 (8,6%)
T3	104 (57,8%)	61 (51,3%)	17 (65,4%)	26 (74,3%)
T4	69 (38,3%)	56 (47,1%)	7 (26,9%)	6 (17,1%)
N				
N1	143 (79.4%)	98 (82.4%)	21 (80,8%)	24 (68,6%)
N2	37 (20.6%)	21 (17.6%)	5 (19,2%)	11 (31,4%)
The degree of tumor differentiation				
G1	14 (7,8%)	8 (6,7%)	4 (15,4%)	2 (5,7%)
G2	105 (58,3%)	65 (54,6%)	15 (57,7%)	25 (71,4%)
G3	61 (33,9%)	46 (38,7%)	7 (26,9%)	8 (22,9%)
Histological type of tumor				
Adenocarcinoma, BDU	170 (94,4%)	111 (93,3%)	26 (100%)	33 (94,3%)
Mucinous adenocarcinoma	6 (3,3%)	4 (3,4%)		2 (5,7%)
Tubular adenocarcinoma	2 (1,1%)	2 (1,7%)		
Adenocarcinoma intestinal type	1 (0,6%)	1 (0,8%)		
Cricoid cell carcinoma	1 (0,6%)	1 (0,8%)		
Type of treatment with adjuvant chemotherapy (ACT)	82 (45,6%)	53 (44,5%)	11 (42,3%)	18 (51,4%)
Observation time, in months	44,5	42,0	52,0	48
Median (lower-upper quartile)	(30,3-60,0)	(27,0-62,8)	(32,0-62,8)	(38,0-57,0)
(min-max)	(1-92)	(1-92)	(4-79)	(1-79)

2. Material and Methods

The object of the study was information about 180 patients treated in the oncological coloproctology department of the Republican Specialized Scientific and Practical Center of Oncology and Medical Radiology in the period from 01.01.2016 to 12/31/2020. The study is retrospective. The criteria for inclusion in the study are primary colorectal cancer, stage III of the disease (N1–N2), a mandatory surgical component of treatment, and the absence of serious concomitant pathology.

To designate a tumor, depending on the localization, the code of the International Classification of Diseases of the 10th revision (ICD-10) was used, according to which C18 is colon cancer, C19 is rectosigmoid compound cancer, C20 is rectal cancer. The international classification of TNM was used to stage the disease. The main characteristics of the patients included in the study are presented in Table 1.

Diagnosis and treatment of patients with CRC was carried out in accordance with the approved by the Ministry of Health of the Republic of Uzbekistan. All patients with morphologically verified rectal cancer underwent preoperative radiation therapy (SOD =54g). After the end of radiation therapy, surgery was performed 8-12 weeks later.

All patients with colon cancer and rectosigmoid junction underwent surgical treatment depending on the location of the tumor. In addition to surgical treatment, for rectal cancer, in addition to radiation and surgical, adjuvant chemotherapy was prescribed according to indications – 82 patients. Adjuvant chemotherapy was performed according to standard XELOX/FOLFIRI regimens. After the end of chemotherapeutic treatment, patients underwent clinical and instrumental examination: ultrasound examination of the pelvic and abdominal organs, fibrocolonoscopy, chest X-ray. The same amount of clinical and instrumental examinations was prescribed to patients who did not receive adjuvant chemotherapy.

The study evaluated the long–term results of treatment of patients with CRC based on the calculation and analysis of survival rates - overall survival (S), progression-free survival (PFS). The starting point in calculating the indicators was the

date of diagnosis, for OV the event was the death of the patient from any cause, for PFS – progressive CRC (distant metastases), for BSV – the death of the patient from CRC, relapse or progression of the disease. The survival rates were calculated using the Kaplan-Mayer method. When comparing two survival curves, a lograng test was used, three or more – Tarone-Ware. The following risk factors for an unfavorable prognosis were considered: gender, age, depth of tumor invasion (T), lesion of lymphatic vessels (N), degree of tumor differentiation (M), lack of adjuvant chemotherapy. A nonparametric Cox proportional risks model was used to assess the impact of risk factors on event-free survival. The multivariate analysis included risk factors that had a significant impact on survival in the monovariate analysis ($p<0.1$). The Wald criterion in multivariate analysis was used to assess the significance of the risk factor, and the likelihood ratio was used to assess the significance of the entire model. The statistical analysis was carried out in the IBM SPSS Statistics 23 program.

3. Results

The five-year overall survival in the study group was 66.4±4.3%, the median survival was not achieved. Figure 1 shows the overall survival rate of patients depending on the localization of the tumor process. Thus, the 5-year of general detectability (GD) in colon cancer was 74.2±4.9%, in rectosigmoid compound cancer – 55.1±10.2%, in rectal cancer – 55.6±10.0%. The median GD was achieved for rectosigmoid junction cancer – 62 months and rectal cancer – 63 months.

The indicators of 5-year GD among men were 65.4±5.6%, among women – 67.3±6.8% (p=0.945). There were no differences in OV when analyzing the effect of the depth of tumor invasion (T), so at T2 the 5-year OV was 71.3±17.1%, at T3 – 67.2±5.7%, at T4 – 65.5±6.7% (p=0.634) and the degree of tumor differentiation (p=0.222). The survival rate of patients under the age of 60 is slightly higher than among patients of older age groups (73.9±6.1% vs 61.0±5.8%, p=0.140). The five-year GD (Figure 2) in the group of patients with N1 was statistically (p=0.001) significantly higher (74.5±4.3%) than in the group of patients with N2 (44.2±9.7%).

Among patients who did not receive ACT, the indicators of 5-year GD are statistically significantly lower than in the group of patients receiving ACT (Figure 3).

The 5-year progression-free survival (PFS) was 59.4±4.0%. A monovariant analysis of the influence of risk factors on PFS revealed that gender (p=0.962), the degree of malignancy of the tumor (p=0.113) and age (p=0.622) are not significant predictors of prognosis. In our study, the following predictors of the prognosis of disease progression (distant metastases) were obtained: the degree of tumor invasion (T4), metastatic lesion of regional lymph nodes (N2) and the absence of adjuvant chemotherapy.

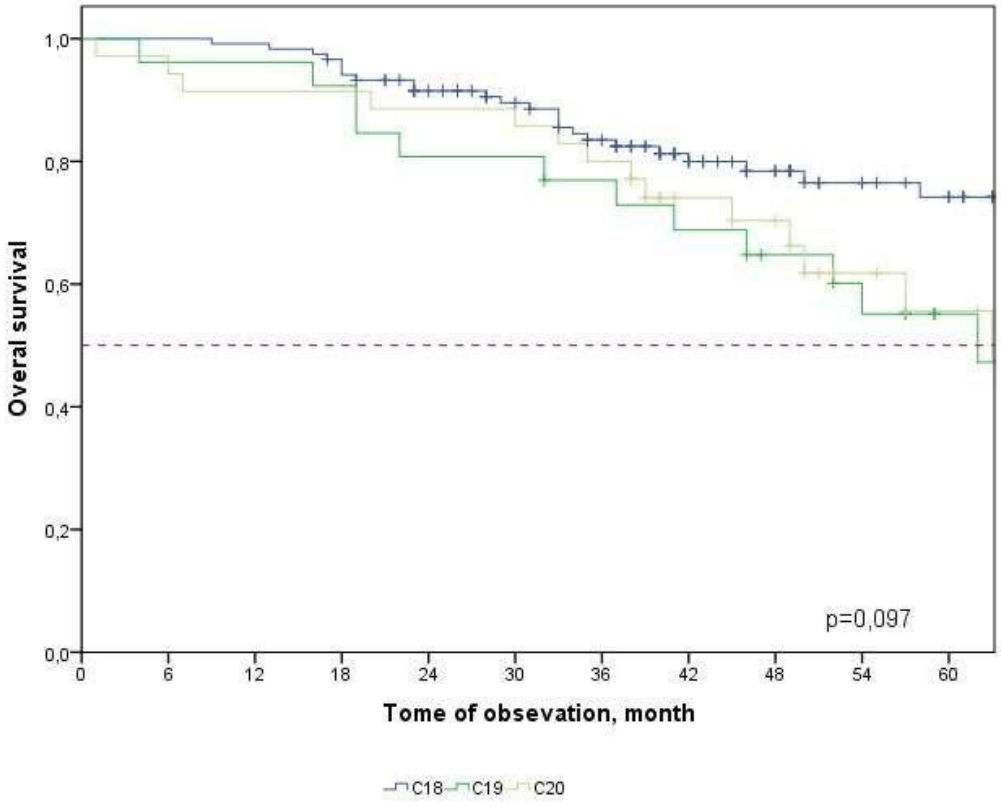

Figure 1. Overall survival of patients with CRC depending on the localization of the tumor process

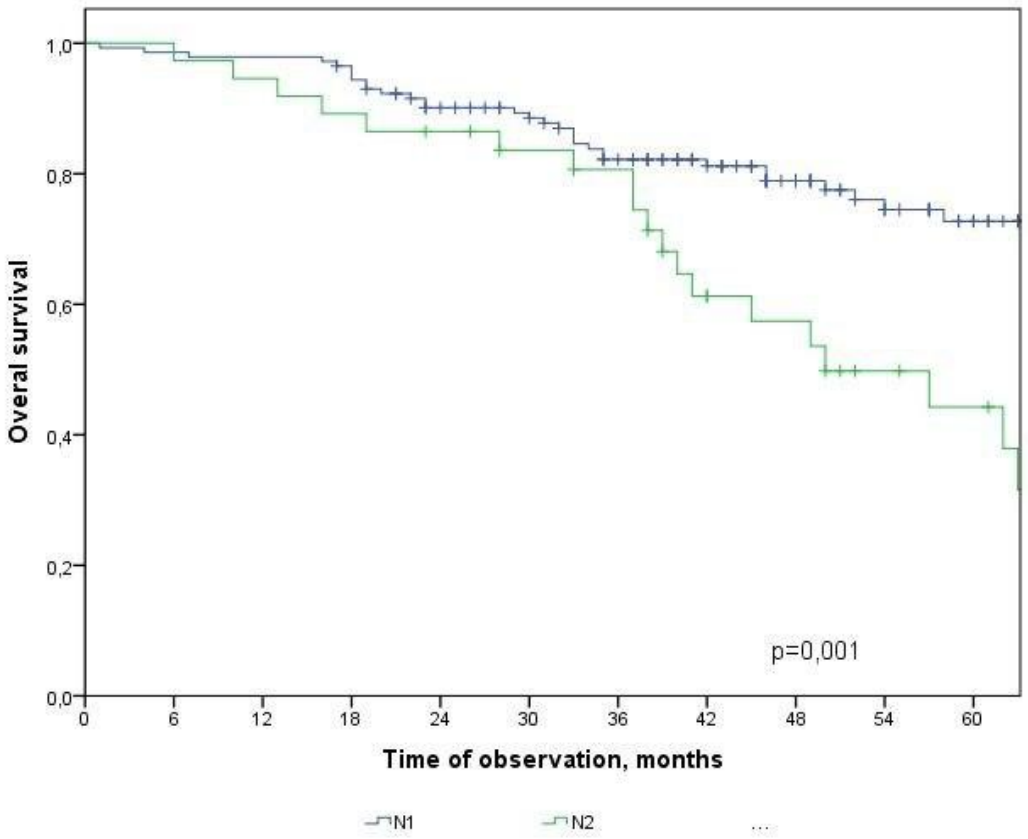

Figure 2. Overall survival of CRC patients depending on the degree of metastatic lesion of regional lymph nodes

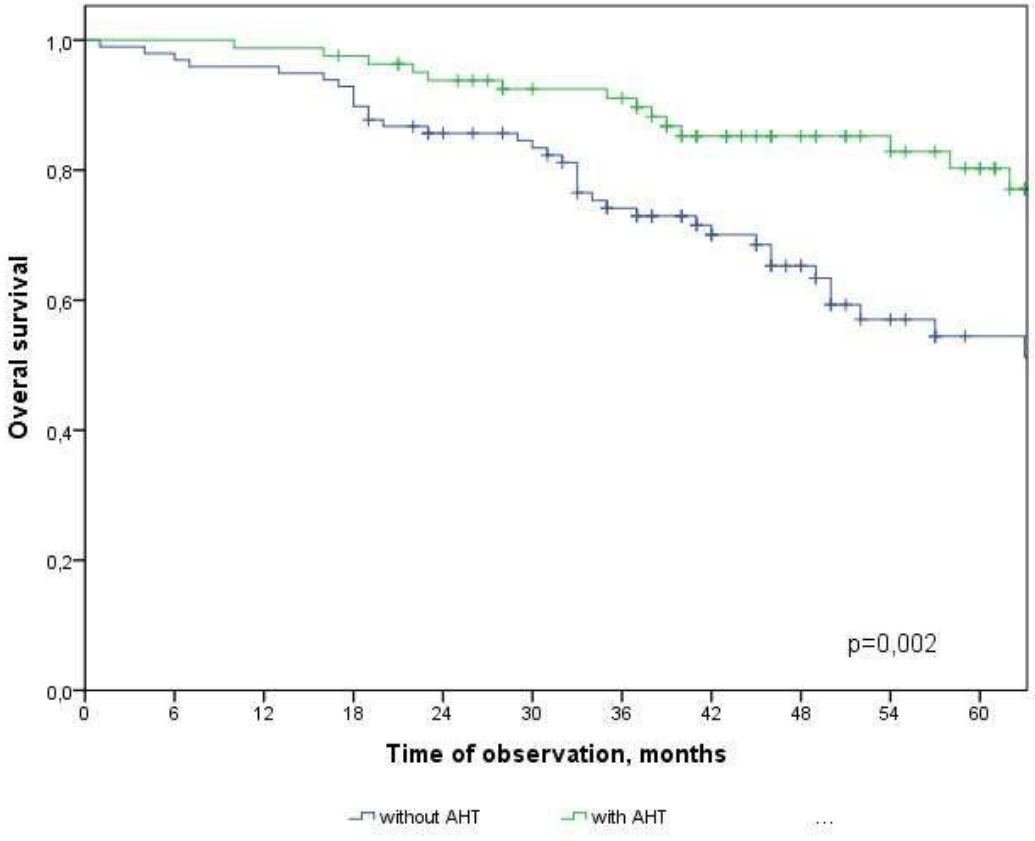

Figure 3. Overall survival of CRC patients depending on the type of treatment

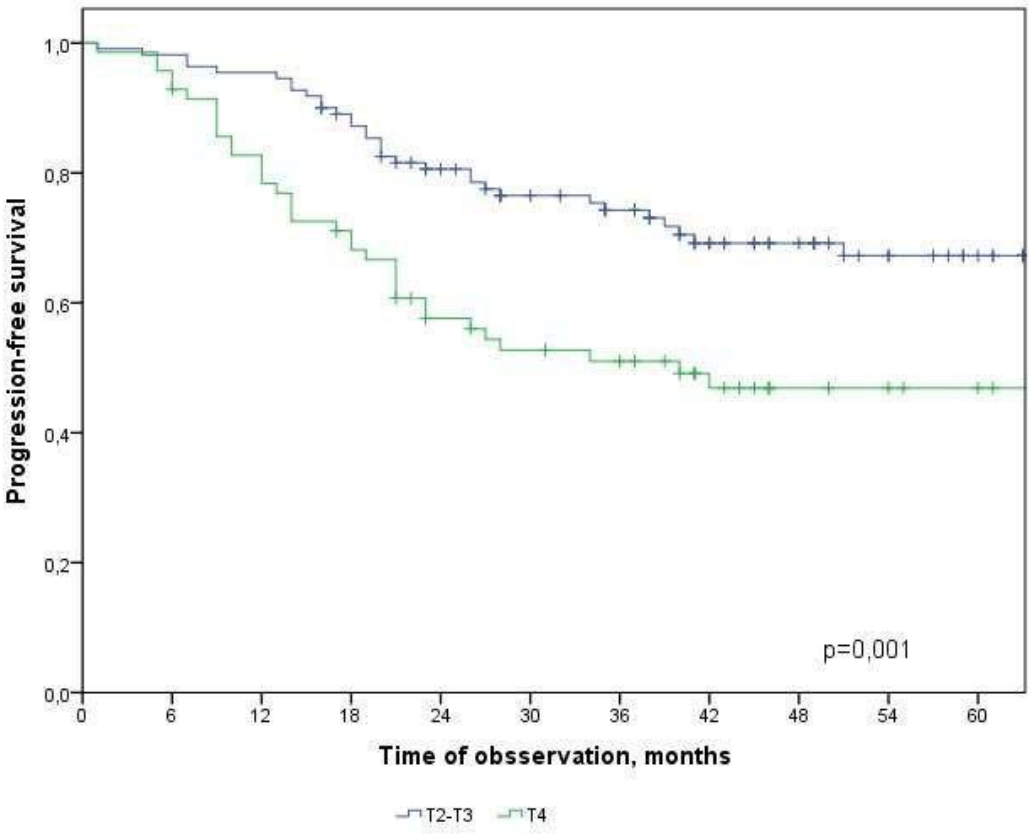

Figure 4. Progression-free survival in CRC patients depending on the depth of invasion

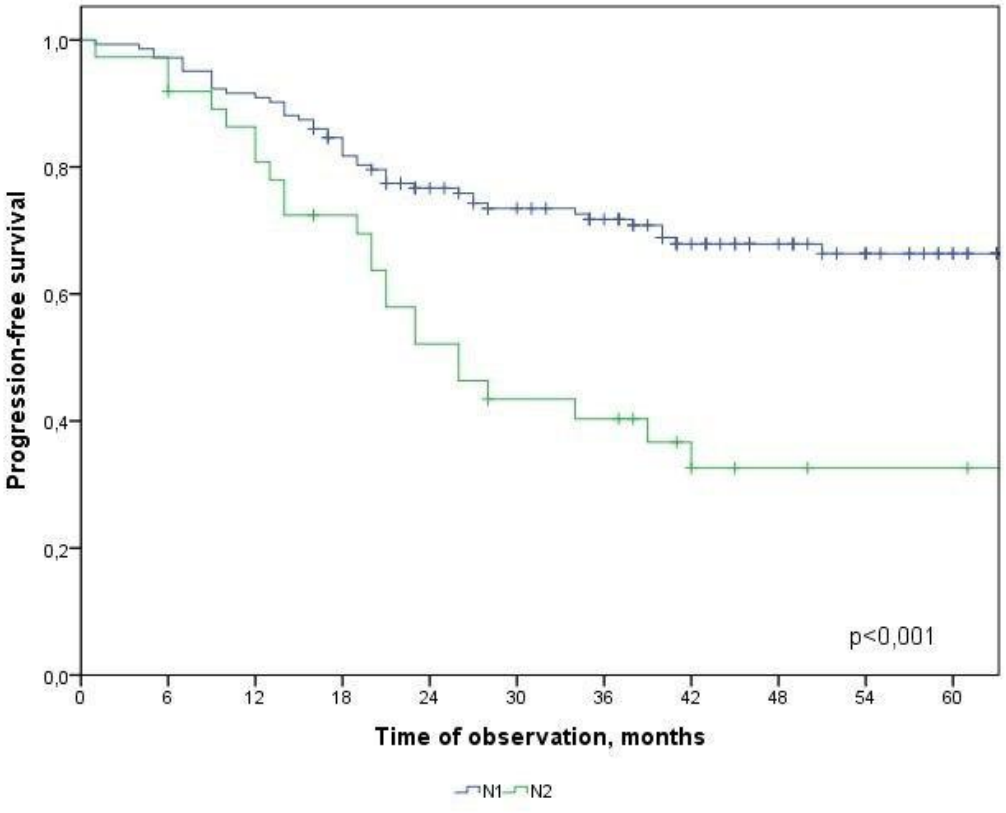

Figure 5. Progression-free survival in CRC patients depending on metastatic lesion of regional lymph nodes

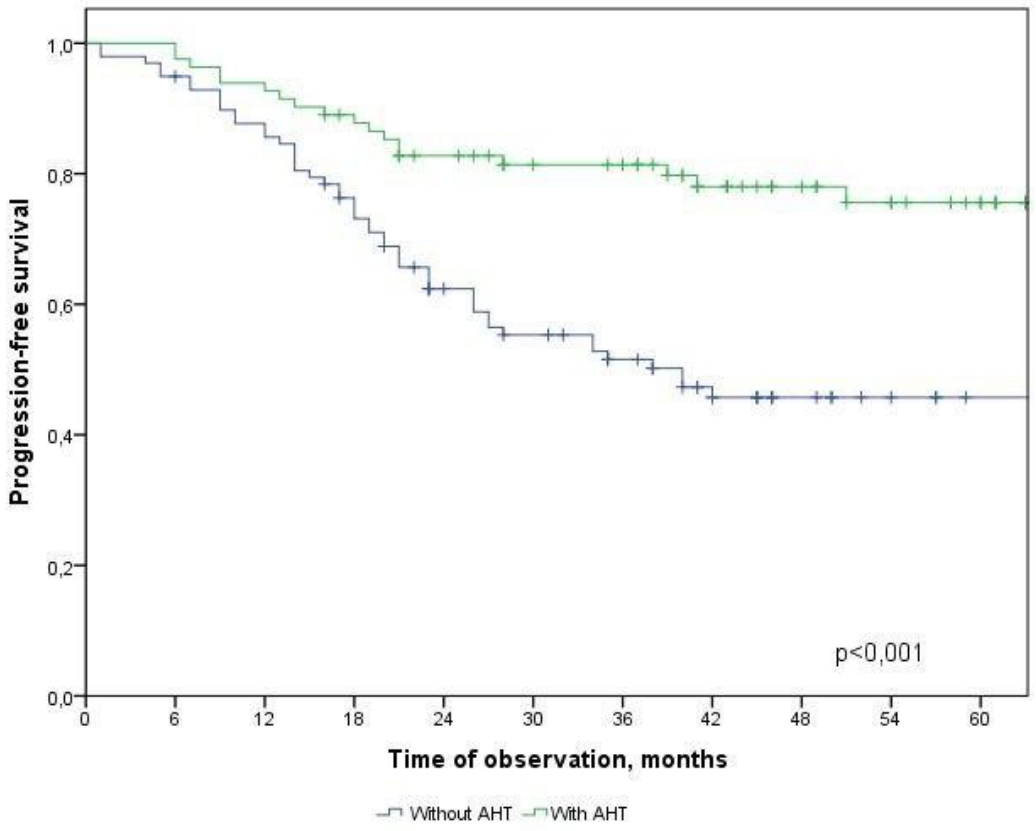

Figure 6. Progression-free survival in CRC patients depending on the type of treatment

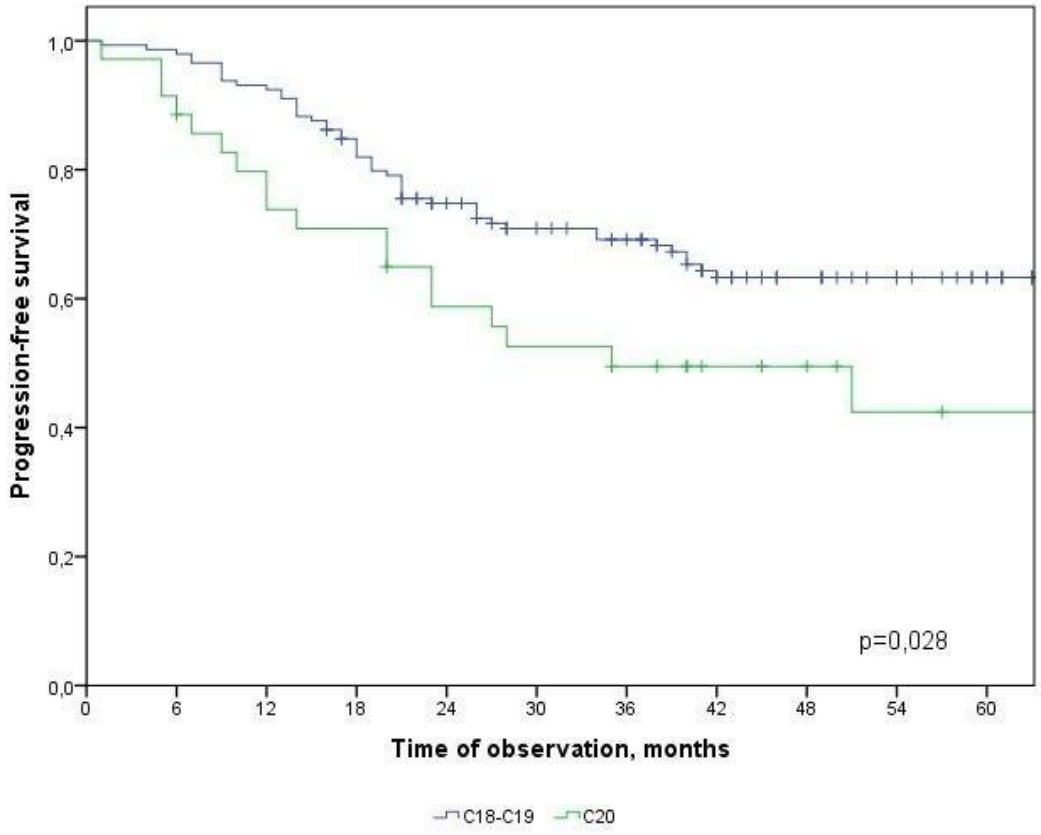

Figure 7. Progression-free survival in CRC patients depending on the primary location of the tumor

Table 2. Multifactorial analysis of the influence of prognostic factors on long-term treatment outcomes of patients included in the study

Risk factors	Regression coefficient, β	The standard error	relative risk (RR) (confidence interval (CI))	Significance level, p
Localization of the C20 tumor	0,792	0,306	2,21 (1,21-4,02)	0,010
The depth of invasion is T4	0,832	0,271	2,29 (1,35-3,91)	0,002
Lymph node lesion N2	0,558	0,271	1,74 (1,03-2,97)	0,040
Absence of ACT	0,788	0,285	2,19 (1,26-3,84)	0,006

Due to the fact that a small number of patients with T2 were included in the study, an analysis of the effects of the depth of invasion of bl was carried out for two groups T2-3 and T4. Thus, in the group of patients with T2-3, 5-year PFS is significantly higher than in the group of patients with T4 (p=0.001), Figure 4.

The survival rate of patients in the group with N1 lymph node lesion is significantly higher than in the group of patients with N2 lesion (p<0.001): 66.4±4.3% and 32.6±8.4%, respectively, Figure 5.

The absence of adjuvant chemotherapy negatively affects the survival of patients without progression (p<0.001): 45.7±5.4% in the group of patients who did not receive ACT and 75.6±5.2% in the group of patients receiving ACT (Figure 6).

To test the hypothesis about the effect of the primary localization of CRC on the prognosis of disease progression, an analysis was performed for two groups: C18-C19 and C20. Thus, the 5-year progression-free survival in the group of patients with primary localization in the rectum is significantly lower (p=0.028) than in the group of patients with primary localization in the colon and rectosigmoid junction (Figure 7).

The following predictors were included in the preliminary model of multivariate analysis of the prognosis of progression-free survival:

ICD: C18-C19 and C20 (x_1)

T2-T3 and T4 (x_2)

N: N1 and N2 (x_3)

ACT: - with ACT и without ACT (x_4)

The results of the multivariate analysis are presented in Table 2, the statistical significance of the model was p<0.001.

In our study, it was shown that the risk of CRC progression increases with: tumor localization C20 (HR=2.21, 95% CI 1.21-4.02, p=0.010), depth of invasion into the intestinal wall T4 (HR=2.29; 95% CI 1.35-3.91, p=0.002), metastic lesion of regional lymph nodes nodes N2 (HR=1.74, 95% CI 1.03-2.97, p=0.040), absence of AHT (HR=2.19; 95% CI 1.26-3.84, p=0.006).

Reducing the number of predictors in the model was performed using the step-by-step elimination method, which did not reveal insignificant predictors. The model equation for expressing significant risk factors for progression has the form:

$$\log(\mathrm{HR}(x)) = 0.792 * x_1 + 0.832 * x_2 + 0.558 * x_3 + 0.788 * x_4$$

4. Conclusions

In the study, the overall survival of CRC patients in the group of patients with N1 was statistically (p=0.001) significantly higher (74.5±4.3%) than in the group of patients with N2 (44.2±9.7%); among patients who did not receive ACT, survival was statistically significantly lower (p=0.002) than in the group receiving ACT.

The study obtained the following predictors of the prognosis of disease progression (distant metastases): the degree of tumor invasion (T4), metastatic lesion of regional lymph nodes (N2) and the absence of adjuvant chemotherapy, which showed a significant effect in multivariate analysis. Thus, the risk of CRC progression increases with: tumor localization C20 (RR=2.21, 95% CI 1.21-4.02, p=0.010), depth of invasion into the intestinal wall T4 (RR=2.29; 95% CI 1.35-3.91, p=0.002), metastic lesion of regional lymph nodes N2 (RR=1.74, 95% CI 1.03-2.97, p=0.040), absence of ACT (RR=2.19; 95% DI 1.26-3.84, p=0.006).

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