

ORIGINAL ARTICLE

CHEMOTHERAPY IN RECTAL CANCER

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ABSTRACT

The aim: To evaluate and analyze early and late results of treatment of patients with rectal cancer after chemotherapy.**Materials and methods:** The study is based on the results of observation of 779 patients with stage II, III and IV rectal cancer (RC) who were divided into groups according to the chemotherapy treatment.**Results:** In the course of chemotherapy treatment of RC patients, most of them received the FOLFOX regimen treatment – 87 patients (43.5%). 40 people (20%) received Mayo regimen. 36 patients (18%) underwent FOLFIRI regimen. Another 33 patients received the XELOX regimen chemotherapy (16.5%). In four cases, patients underwent Tegafur monotherapy (2%).**Conclusions:** The obtained data for patients with stage III RC showed that at all studied time intervals, the highest percentage of surviving patients was recorded in those who received chemotherapeutic treatment according to the FOLFOX regimen. In patients with stage II RC, the most effective was Mejo regimen – 30.7% (survived patients for the 5 year observation).**KEY WORDS:** complex treatment of rectal cancer, rectal cancer, chemotherapy treatment of cancer

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INTRODUCTION

Every year, about 100 thousand new cases of rectal cancer (RC) are diagnosed in Europe, in the USA – more than 40 thousand [1,2].

According to the National Cancer Registry of Ukraine, in the structure of the incidence of malignant neoplasms (MN) of the population of Ukraine (excluding non-melanoma skin MN), RC accounts for 5.4% among women, and 6.8% among men. 6.1% of women and 7.2% of men aged 55-74 suffer from RC. 7.3% of women over 75 years have this disease.

In the structure of mortality of the Ukraine's population from MN, RC was diagnosed in 6.2% of men aged 55-74 years, and in 9.1% of those who are 75 and older. Among women of 75 years and older – in 8.4% (2018 – updated information).

According to the National Cancer Registry of Ukraine, in 2019, 23.7% and 19.7% of the initially identified patients with RC had stage III and IV, respectively. 72.1% of patients underwent special treatment in 2019. Mortality up to one year was 25.4% [3].

Combination therapy is the main method of treatment of rectal cancer patients. It includes surgical treatment, radiation and polychemotherapy (PCT) in different sequences [4,5].

Rectal cancer has long been considered a radioresistant tumour. However, significant progress has been made in recent years in the treatment of RC patients through the use of neoadjuvant chemotherapy (NACT). This approach allows

to obtain satisfactory results and regression of the primary tumour in patients with stages I-II of the disease [6,7].

For about 30% of patients with locally advanced RC, the performance of sphincter-preserving surgical intervention is impossible [8]. There is no definitive treatment and diagnostic standard for locally advanced RC (LARC), unlike for localized forms. For a long time, total mesorectumectomy and fluoropyrimidine-based NACT have been used in the treatment of patients with LARC [9]. Radiation therapy (RT) overregulates with one of the enzymes of activation of fluoropyrimidines thymidine phosphorylase within the tumour, which explains the effectiveness of FU/CAP [10, 11, 12]. Oxaliplatin is also a promising drug in the treatment of patients; in a number of studies, it has demonstrated potential as a radiosensitizing agent [13, 14, 15]. The safety and efficacy of the combination of CAP and XELOX in patients with LARC currently need further study.

According to “the NCCN Clinical Practice Guidelines in Oncology: Colon Cancer”, chemotherapy is indicated for patients with stage II RC in the case of adverse factors, namely the FOLFOX-6 regimen. Capecitabine and 5-FU for these patients are similar in efficacy, with no proven benefit of oxaliplatin addition.

FOLFOX-6 and CapeOX show greater efficacy at stage III RC compared to the Mejo regimen.

According to the NCCN recommendations, the duration of chemotherapy treatment is 6 months. CT in patients over 75 years of age with stage III RC should be based on the presence of concomitant pathology.

Table I. Overall survival rates of patients with rectal cancer (%) II stage

Time of observation, month	% of patients survived				Standard error			
	FOLFIRI	FOLFOX	XELOX	Mejo	FOLFIRI	FOLFOX	XELOX	Mejo
6	96,9	98,4	89,3	97,9	±4,3	±2,3	±10,2	±2,9
12	90,6	96,3	65,1	95,9	±7,3	±3,6	±18,7	±4,0
24	68,4	68,5		74,4	±12,4	±9,9		±9,0
36	54,3	52,7		53,5	±14,3	±11,1		±10,6
48	21,7	43,1		37,6	±13,2	±11,5		±10,8
60	5,4	23,5		30,7	±7,4	±12,4		±10,8

Table II. Overall survival rates of patients with rectal cancer (%) III stage

Time of observation, month	% of patients survived				Standard error			
	FOLFIRI	FOLFOX	XELOX	Mejo	FOLFIRI	FOLFOX	XELOX	Mejo
6	96,0	98,3	95,7	94,4	±5,5	±2,4	±6	±7,6
12	78,5	89,4	90	61,1	±12	±6,4	±9,6	±16,2
24	42,1	54,2	37,5	39,6	±17	±12,1	±20,4	±17,8
36		32,5		27,5		±16,8		±15,9
48				16,5				±12,8

Table III. Overall survival rates of patients with rectal cancer (%)

Time of observation, month	% of patients survived				Standard error			
	FOLFIRI	FOLFOX	XELOX	Mejo	FOLFIRI	FOLFOX	XELOX	Mejo
6	97,2	99,3	96,7	95,0	±2,8	±0,9	±3,2	±3,4
12	85	87,7	79,2	84,9	±6,2	±4,2	±8,4	±5,7
24	58,1	56,7	39,3	57,4	±9,5	±7,1	±12,6	±8,1
36	33,5	42,5	9,2	43,8	±10,1	±7,6	±10,7	±8,4
48	13,4	30,8		33,2	±8,4	±8,0		±8,3
60	3,4	14,2		28,0	±4,6	±7,8		±8,5

Table IV. Age structure of patients in correlation with the chemotherapy regimen

Regimen of chemotherapy treatment	Average age of patients		
	II stage	III stage	IV stage
FOLFIRI	60,6±8	56,2±7,8	63,2±4,5
FOLFOX	58,9±10,1	59,8±9,9	59,1±6,6
XELOX	56,1±12	52,3±12,4	55,1±6,8
Majo	56,6±10,3	53,2±16,6	60,3±7,3
Tegafur	63±8,5	-	72

Table V. The effectiveness of the FOLFOX regimen at different stages of rectal cancer

Time of observation, month	% of patients who survived the FOLFOX treatment regimen		
	II stage	III stage	II-IV stage
6	98,4	98,3	99,3
12	96,3	89,4	87,7
24	68,5	54,2	56,7
36	52,7	32,5	42,5
48	43,1		30,8
60	23,5		14,2

Table VI. The effectiveness of the FOLFIRI regimen at different stages of rectal cancer

Time of observation, month	% of patients who survived the FOLFIRI treatment regimen		
	II stage	III stage	II-IV stage
6	96,9	96,0	97,2
12	90,6	78,5	85
24	68,4	42,1	58,1
36	54,3		33,5
48	21,7		13,4
60	5,4		3,4

Table VII. The effectiveness of the XELOX regimen at different stages of rectal cancer

Time of observation, month	% of patients who survived the XELOX treatment regimen		
	II stage	III stage	II-IV stage
6	89,3	95,7	96,7
12	65,1	90	79,2
24		37,5	39,3
36			9,2
48			
60			

Table VIII. The effectiveness of the Mejo regimen at different stages of rectal cancer

Time of observation, month	% of patients who survived the Mejo treatment regimen		
	II stage	III stage	II-IV stage
6	97,9	94,4	95,0
12	95,9	61,1	84,9
24	74,4	39,6	57,4
36	53,5	27,5	43,8
48	37,6	16,5	33,2
60	30,7		28,0

At present, evidence-based medicine does not provide a definitive answer as to the appropriateness of CT in stage II RC and in elderly patients.

THE AIM

The aim was to evaluate and analyze early and late results of treatment of patients with rectal cancer after chemotherapy.

MATERIALS AND METHODS

The study is based on the results of observation of 779 rectal cancer (RC) patients who were treated in the municipal institution "Precarpathian Clinical Oncology Centre" for the period during 2012-2018.

The early and late results of chemotherapy treatment of rectal cancer were studied and evaluated.

All patients were divided according to the stage of the disease (TNM system), and patients with stage II, III, and IV rectal cancer were included into the study. We analyzed the obtained results by comparing the studied indicators within each of the stages of colon cancer and together for

the total number of patients, determining their impact on survival.

RESULTS

ANALYSIS OF THE OVERALL SURVIVAL OF PATIENTS WITH STAGE II RC ACCORDING TO THE PCT REGIMEN

Patients with stage II RC accounted for 67.8% of the total number of patients (528 people). 97.2% of them underwent special treatment (513 patients). 67 patients (12.7%) underwent surgical treatment. Surgery + chemotherapy was prescribed to 32 people, which is 6.1%. 15 patients (2.8%) received chemotherapy as an independent method of treatment. 144 patients received radiation therapy as an independent method, which is 27.3%. Another 34 patients had the following treatment: surgery + chemotherapy + radiation therapy (6.4%). 213 patients (40.3%) received surgical + radiation treatment. Chemotherapy + radiation treatment was prescribed for 1.5% of patients (8 people).

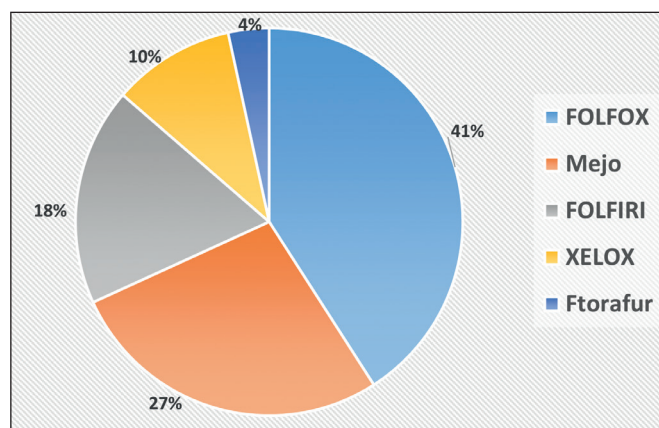


Fig. 1. Structure of chemotherapeutic treatment of stage II RC

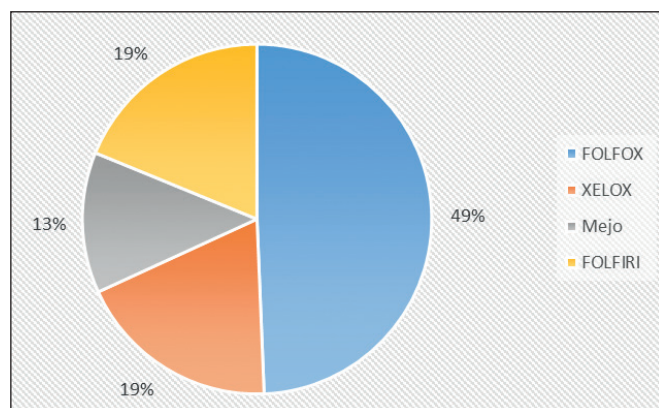


Fig. 3. Structure of chemotherapeutic treatment of stage III RC

Of all these groups, 88 patients with unfavourable prognostic factors, according to NCCN, received totally chemotherapy.

In the structure of chemotherapeutic treatment of stage II RC, most patients followed FOLFOX treatment regimen – 36 patients (40.9%). Mejo was received by 24 people, which is 27.3%. 16 patients (18.2%) underwent FOLFIRI treatment regimen. Another 9 patients followed the XELOX chemotherapy regimen (10.2%). In three cases, patients received Tegafur monotherapy (3.4%) (Fig. 1).

For comparative analysis of the effectiveness of the RC chemotherapy regimen in patients with stage II, the first group of patients received FOLFIRI treatment regimen, the second group followed FOLFOX, the third group consisted of patients who received chemotherapy according to Mejo regimen, and the fourth group followed XELOX treatment regimen. Indicators of overall cumulative survival in patients of these groups are shown in Fig. 2 (Cumulative survival of RC patients according to the chemotherapy treatment regimen).

In Table I a detailed comparative analysis of the percentage of patients who survived treatment with FOLFIRI, FOLFOX, Mejo and XELOX PCT regimens is presented; these regimens are compared at identical intervals.

A comparative analysis of patient survival rates was started at the sixth month of follow-up, with the highest percentage of surviving patients recorded in the FOLFOX group (98.4%); slightly worse results were in the group of

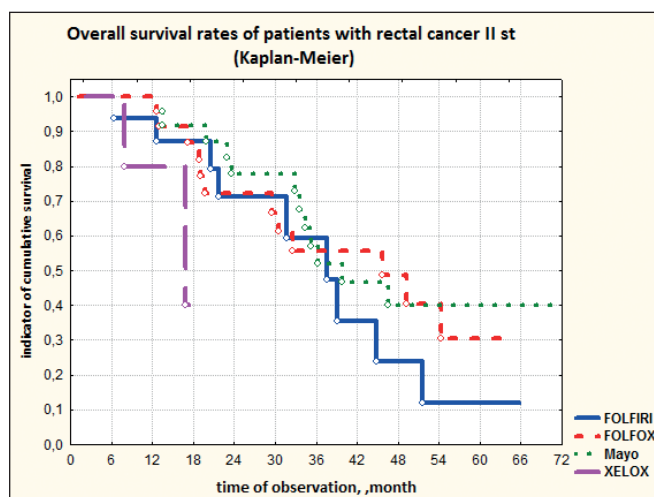


Fig. 2. Cumulative survival of patients with stage II RC according to the chemotherapeutic treatment regimen

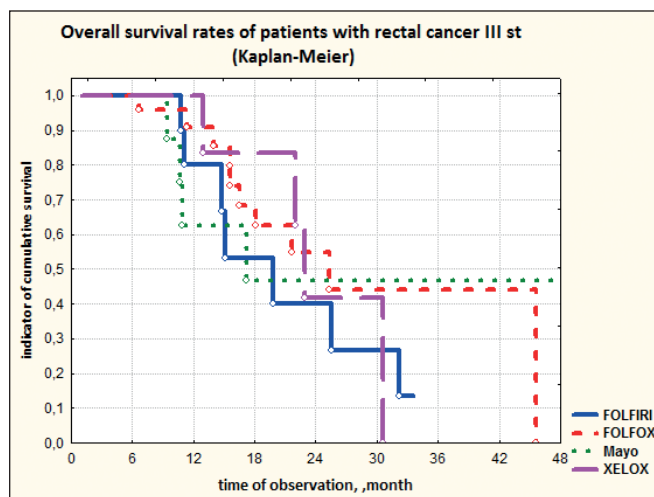


Fig. 4. Cumulative survival of patients with stage III RC according to the chemotherapeutic treatment regimen

patients receiving Mejo chemotherapy regimen – 97.9% of survivors. The lowest patient survival rate was recorded in the XELOX group, namely – 89.3%.

At the 12th month of follow-up, this trend continued: in the groups of patients who followed FOLFOX and Mejo regimens, the same survival rates were observed: 96.3% and 95.9%, respectively. The worst indicators were in the XELOX group – 65.1%.

A two-year follow-up showed that the highest percentage of surviving patients was registered in the Mejo group – 74.4%, slightly worse results were in the groups of patients receiving FOLFOX and FOLFIRI chemotherapy – 68.5% and 68.4%, respectively. There were no patients receiving XELOX treatment.

At the 36th month of follow-up, the percentage of surviving patients in the FOLFOX, FOLFIRI and Mejo treatment groups was virtually the same: 52.7%, 54.3% and 53.5%, respectively.

At the 48th month of follow-up, the highest percentage of surviving patients was recorded in the FOLFOX group (43.1%), the worst results were in patients who underwent PCT according to the FOLFIRI regimen (21.7%).

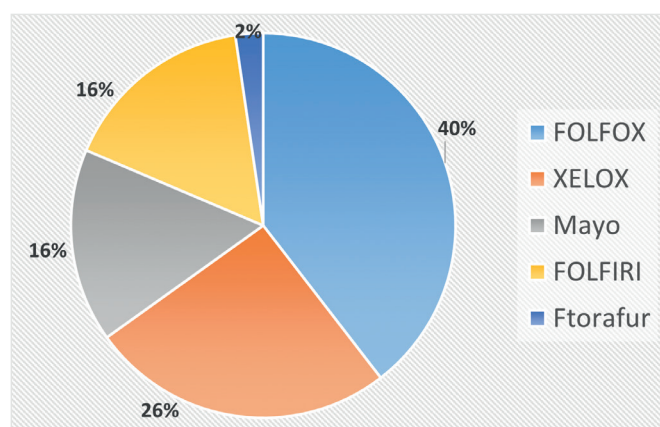


Fig. 5. Structure of chemotherapeutic treatment of stage IV RC

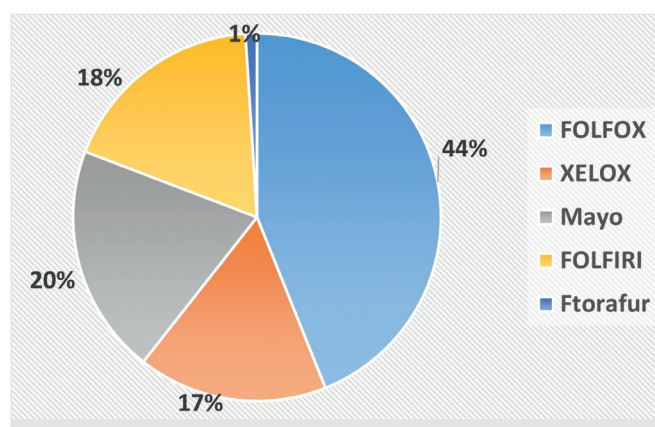


Fig. 6. Structure of chemotherapeutic treatment of stage I-IV RC

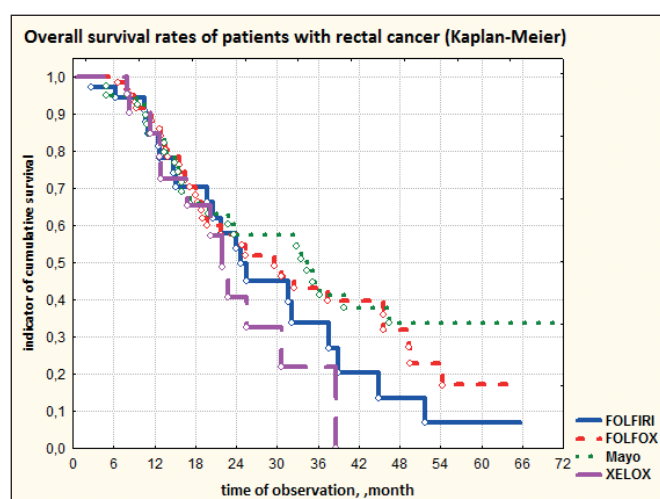


Fig. 7. Cumulative survival of patients with RC according to the chemotherapy treatment regimen

The last comparative analysis was performed at the 60th month of follow-up: the highest percentage of surviving patients was registered in the Mayo group (30.7%), slightly worse – in the FOLFOX group (23.5%), the worst – in patients with PCT according to FOLFIRI regimen (5.4%).

ANALYSIS OF THE OVERALL SURVIVAL OF PATIENTS WITH STAGE III RC ACCORDING TO THE PCT REGIMEN

Patients with stage III RC accounted for 18.7% of the total number of patients (146 people). Of these, 97.9% underwent special treatment (143 patients). 17 patients (11.6%) received surgical treatment. 19 people (13%) had surgery + chemotherapy. 3 patients (2%) received chemotherapy as an independent method of treatment. Radiation therapy, as an independent method, was followed by 9 patients (6.2%). Another 38 patients underwent surgery + chemotherapy + radiation therapy (26%). 48 patients (32.9%) received surgical + radiation treatment. Chemotherapy + radiation treatment was prescribed to 6.2% of patients (9 people).

Of all these groups, 69 patients totally received chemotherapy.

In the structure of chemotherapy treatment of patients with stage III RC, the majority of patients received FOLFOX treatment – 34 persons (49.3%) out of 69 patients who underwent chemotherapeutic treatment. 13 patients (18.8%) received chemotherapy treatment according to FOLFIRI and XELOX regimens. Another 9 patients had monotherapy according to the Mayo regimen (13%) (Fig. 3).

For the comparative analysis of the effectiveness of the chemotherapeutic treatment regimen of RC in patients with stage III, the first group of patients received FOLFIRI regimen, the second group consisted of the patients who followed FOLFOX regimen, the third group received XELOX, and the fourth group followed Mayo regimen.

Indicators of overall cumulative survival in patients of these groups are shown in Fig. 4 (Cumulative survival of patients with stage III RC according to the chemotherapeutic treatment regimen).

In Table II a detailed comparative analysis of the percentage of patients who survived treatment with FOLFIRI, FOLFOX, XELOX and Mayo PCT regimens is presented; these regimens are compared at identical intervals.

A comparative analysis of patient survival rates was started at the sixth month of follow-up, with the highest percentage of surviving patients recorded in the FOLFOX group (98.3%); slightly worse results were in the group of patients receiving FOLFIRI chemotherapy regimen – 96.0% of survivors. The lowest patient survival rate was registered in the Mayo group, namely 94.4%.

Subsequent one-year follow-up showed the following data: the highest survival rates were in patients in the XELOX and FOLFOX groups, and the worst ones were in the FOLFIRI group.

At the 24th and 36th month of follow-up, the highest percentage of surviving patients was observed in the FOLFOX group: 54.2% and 32.5%, respectively. From the 36th month, only those patients who received treatment according to the FOLFOX and Mayo regimens remained under observation.

In fact, at all time intervals, the highest percentage of surviving patients was registered in the FOLFOX group, but at the 36th month of follow-up, there were only 2 persons who followed the Mayo treatment (16.5% of surviving patients).

ANALYSIS OF THE OVERALL SURVIVAL OF PATIENTS WITH STAGE IV RC ACCORDING TO THE CHEMOTHERAPY TREATMENT

Of the 779 rectal cancer (RC) patients who had been treated at the municipal institution "Carpathian Clinical Oncology Centre" for the period during 2012-2018, 105 patients (13.5%) had stage IV RC. 88 of them (83.8%) underwent special treatment. 31 patients (29.5%) received surgical treatment. 19 people (18.1%) followed surgery + chemotherapy. 13 people (12.4%) received chemotherapy as an independent method of treatment. Radiation therapy, as an independent method, was received by 11 patients (10.5%). Another 8 patients underwent surgery + chemotherapy + radiation therapy (7.6%). 3 patients (2.9%) received surgical + radiation therapy, and the same number of patients (2.9%) had chemotherapeutic + radiation treatment.

Of all these groups, 43 patients totally received chemotherapy.

FOLFOX and XELOX regimens were dominant in the structure of chemotherapeutic treatment – 39.5% (17 patients) and 25.6% (11 patients), respectively.

Mejo and FOLFIRI regimens were followed by the same number of patients: 16.3% (7 patients); in one case patients received Tegafur monotherapy (2.3%) (Fig. 5).

A comparative analysis of the effectiveness of chemotherapeutic treatment regimens in patients with stage IV RC was not performed because of the insufficient number of patients with chemotherapeutic treatment for adequate statistical analysis.

ANALYSIS OF THE OVERALL SURVIVAL OF PATIENTS WITH RC ACCORDING TO THE PCT REGIMEN, REGARDLESS OF THE STAGE OF THE DISEASE

773 RC patients took part in the follow-up; of these, 744 patients (96.2%) underwent special treatment. 115 patients (15.5%) received surgical treatment. 70 people (9.4%) had surgery + chemotherapy. 31 patients (4.2%) received chemotherapy as an independent method of treatment. Radiation therapy, as an independent method, was prescribed to 164 patients (22%). Another 80 patients (10.8%) underwent surgery + chemotherapy + radiation therapy. 264 patients (35.5%) received surgical + radiation treatment. Chemotherapy + radiation treatment were prescribed to 2.7% of patients (20 people).

200 patients from all these groups totally underwent chemotherapy.

87 RC patients (43.5%) followed FOLFOX regimen in the structure of chemotherapeutic treatment. 40 people (20%) received Mejo regimen. FOLFIRI was prescribed to 36 patients, which is 18%. Another 33 patients (16.5%) received chemotherapy with the XELOX regimen. In four cases, patients underwent Tegafur monotherapy (2%) (Fig. 6).

For comparative analysis of the effectiveness of the chemotherapy treatment regimen in RC patients, four study groups were formed: the FOLFIRI, FOLFOX, XELOX and Mejo. Indicators of overall cumulative survival analysis of

patients of these groups are shown in Fig. 7 (Cumulative survival of patients with RC according to the chemotherapy treatment regimen).

In Table III a detailed comparative analysis of the percentage of patients who survived treatment with FOLFIRI, FOLFOX, XELOX and Mejo PCT regimens is presented; these regimens are compared at identical intervals.

A comparative analysis of patient survival rates was started at the sixth month of follow-up, with the highest percentage of surviving patients recorded in the FOLFOX group (99.3%); slightly worse results were in the group of patients receiving FOLFIRI chemotherapy regimen – 97.2% of survivors. The lowest patient survival rate was registered in the Mejo group, namely 95.0%.

At the 24th and 36th month of follow-up, the highest percentage of surviving patients was observed in the FOLFOX group: 54.2% and 32.5%, respectively. From the 36th month, only those patients who received treatment according to the FOLFOX and Mejo regimens remained under observation.

At the 12th month of follow-up, the following data were obtained: the highest percentage of surviving patients was recorded in the FOLFOX group (87.7%); slightly worse results were in the groups of patients receiving FOLFIRI and Mejo chemotherapy regimens – 85% and 84.9% of survivors, respectively. The lowest patient survival rate (79.2%) was recorded in the XELOX group.

At a subsequent two-year follow-up, almost identical survival rates were recorded in the FOLFIRI, FOLFOX and Mejo groups – 58.1%, 56.7% and 57.4%, respectively; and significantly worse results were in the group of patients receiving chemotherapy treatment according to the XELOX regimen – 39.3% of survivors.

At the 36th month of follow-up, the percentage of surviving patients in the FOLFOX and Mejo treatment groups was virtually the same: 42.5%, 43.8%, respectively; slightly worse results were in the FOLFIRI group (33.5%). Significantly worse results were in the group of patients receiving chemotherapy with the XELOX regimen – 9.2% of survivors.

At the 48th month of follow-up, the highest percentage of surviving patients was recorded in the Mejo group (33.2%); slightly worse results were in RC patients following the FOLFOX regimen (30.8%), the worst results were in RC patients who were treated according to the FOLFIRI regimen (13.4%). There were no follow-up patients receiving XELOX treatment.

The last comparative analysis was performed at the 60th month of follow-up: the highest percentage of surviving patients was recorded in the Mejo group (28.0%), slightly worse results were in the FOLFOX group (14.2%), and the worst data were in RC patients following the FOLFIRI regimen (3.4%).

ANALYSIS OF PATIENTS' AGE AND PCT REGIMEN

Aging is a progressive multi-organ reduction of the body's functional reserves with a corresponding decrease in tolerance to stress, including chemotherapy (CT). There is a

decrease in the reserves of red bone marrow and metabolic properties of the liver. So, these circumstances increase the risk of side effects of CT in the elderly.

Age-related decline in bone marrow reserves causes the development of unpredictable myelotoxicity and an increase in the incidence of deep neutropenia on the background of standard chemotherapeutic regimens (5-FU + leucovorin ± irinotecan, FOLFOX). The XELOX regimen does not show an increase in toxicity to the elderly. The analysis of patients' age and the prescribed regimen of chemotherapeutic treatment was carried out (Table IV).

DISCUSSION

To better understand the results of chemotherapeutic treatment of patients, the analysis of the effectiveness of the FOLFOX regimen at different stages of RC (Table V), FOLFIRI regimen at different stages of RC (Table VI), XELOX regimen at different stages of RC (Table VII), Mejo regimen at different stages of RC (Table VIII), and also the analysis of patients' age structure in correlation with the received chemotherapeutic treatment was carried out.

When analyzing the age of patients and the PCT regimen, the identity for stages II and IV RC was noticed; Tegafur monotherapy was prescribed to older patients, as the choice of CT regimen was based on the following principles: the patient's ability to tolerate chemotherapy, the benefit-harm ratio of anticancer therapy in the particular case (taking into account concomitant pathology), the impact of cancer on the duration and quality of life of the patient.

Further analysis was performed on correlations between the following study parameters: colon cancer stage, treatment received (surgery, chemotherapy), status (registered, deceased), sex of patients, localization of the primary tumour. The observed correlations are significant at $p < 0.05000$.

The most significant correlative dependence was between:

- stage and treatment (744 observations, $p = 0.000000$);
 - localization of the primary tumour and chemotherapy treatment (200 observations, $p = 0.021463$);
 - sex and treatment, (744 observations, $p = 0.007464$);
- No relationship was found between:
- sex and chemotherapy treatment, (200 observations, $p = 0.582047$);
 - stage and chemotherapy treatment (200 observations, $p = 0.224006$);
 - status and chemotherapy treatment (200 observations, $p = 0.347195$).

CONCLUSIONS

According to the results, the overall survival of patients correlates with the stage of RC and chemotherapy treatment regimen.

In patients with stage II colon cancer the most effective PCT regimen was Mejo – 30.7% of patients who survived at 5 years of follow-up.

For patients with stage III RC, at all time intervals, the highest percentage of surviving was in those who followed the FOLFOX chemotherapy, but at the 36th month only 2 people who received Mejo treatment stayed alive (16.5% of surviving patients).

Analyzing the data obtained in RC patients, without graduation at the stage it can be stated that at the 60th month of follow-up the highest percentage of surviving patients was recorded in the Mejo group (28.0%), slightly worse results were in the FOLFOX group (14, 2%), the worst results were in RC patients according to the FOLFIRI regimen (3.4%).

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Conflict of interest:

The Authors declare no conflict of interest.

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