

Impact of Complications after Surgical Treatment of Colon Cancer on Survival

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ABSTRACT

Objective: The aim of our study was to analyze the postoperative complications by grouping into surgical and non-surgical as well as to study their impact on 5-year overall survival (OS) and 3-year disease free survival (DFS). **Methods:** A retrospective study was conducted 550 patients who underwent surgery for colon cancer between 2015-2019 in the "Multidisciplinary medical center" of the city Nur-Sultan (Kazakhstan). The cohort was divided into 3 groups: patients with surgical complications, non-surgical complications and no complications. The Kaplan-Meier curve was made to compare OS and DFS between groups. Cox regression was used to study the effect of factors on survival. **Results:** In stage I colon cancer, the OS rate was 88.9% in the group without complications, 60% in the group with surgical complications, 65.5% in the group with non-surgical complications ($p < 0.05$). DFS was 88.3%, 60% and 65.5%, respectively ($p < 0.05$). In stage II colon cancer, OS rate was 85% in the group without complications, 60% in the group with surgical complications, 65% in the group with non-surgical complications ($p < 0.05$). DFS was 85%, 59.4% and 50%, respectively ($p < 0.05$). In stage III colon cancer, OS rate was 81.5% in the group without complications, 42.6% in the group with surgical complications, 59.3% in the group with non-surgical complications ($p < 0.05$). DFS was 81.5%, 42.6% and 59.3%, respectively ($p < 0.05$). In multivariate analysis, both surgical and non-surgical complications were found to be risk factors for decreased OS, as well as for decreased DFS.

Conclusion: Surgical and non-surgical complications had a negative impact on OS and DFS.

Keywords: Postoperative complications, colon cancer, survival

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INTRODUCTION

According to the International Agency for Research on Cancer's report, colorectal cancer is recognized as one of the most common types of cancer in the world. It is estimated that in the world there are 10.2% of newly diagnosed and 9.2% of deaths from this disease (1). In recent years, in the Republic of Kazakhstan there is an increase in the incidence and mortality from colon cancer (2). Also, in Kazakhstan in the structure of oncopathology colon cancer takes the 5th place and over 1600 new cases of colon cancer are reported annually (3). Surgery is the main treatment of the colon cancer (4-8). According to the results of some studies, postoperative complications occur in most patients after surgery (9-11). Postoperative complications impact on the long-term outcome (12-13). Consequently, much attention has recently been paid to studying the effect of postoperative complications on the survival of cancer patients (14-16). Previous studies were aimed at studying complications according to the classification of Clavien-Dindo (14,17,18). The effects of infective and non-infective postoperative complications on survival were also investigated (18-19). Other authors study postoperative complications on severity and number (20). The aim of our study was to analyze the postoperative complications by grouping into surgical and non-surgical as well as to study their impact on 5-year overall survival (OS) and 3-year disease free survival (DFS).

PATIENTS AND METHODS

The study was conducted in the "Multidisciplinary medical center" of the city Nur-Sultan (Kazakhstan) between 2015-

2019 years. Data were extracted from Integrated Medical Information System. The structure of the research work meets modern ethical standards and requirements. Study protocol was approved by ethics committee. Inclusion criterion: patients with a verified diagnosis of stage I-III colon cancer after surgery. Exclusion criterion: patients with a verified diagnosis of stage IV colon cancer, rectal cancer. The following data were analyzed: age, gender, staging according to the international classification of TNM, tumor grade, tumor location, body mass index (BMI), surgery, type of complication, concomitant morbidities, overall survival and disease free survival.

Age was classified as <65, 65-74 and >75 years. Also, all complications were divided into surgical, directly related to surgery (anastomotic leakage, ileus, intra-abdominal infection, sepsis, bleeding) and non-surgical, complications indirectly associated with surgery (pneumonia, electrolyte disorders, delirium, diarrhea, constipation, malnutrition). The described complications occurred in the first month after surgery. Concomitant morbidities: cardiovascular and respiratory system, gastrointestinal tract.

A 5-year overall survival and 3-year disease-free survival were the final assessment points. Overall survival was defined as the time from surgery to death for any reason or until the end of the medical observation. The disease-free interval was defined as the time from surgery to relapse or as the time from surgery to the end of medical observation or death in the absence of relapse. The medical observation was completed on December 1, 2019. *Statistical analysis*

The mean with standard deviation was applied to assess continuous variables. Chi-squared test was used to compare groups. p value less than 0.05 was deemed to be a statistically significant value. The Kaplan-Meier curve was made to compare overall survival between patients without complications, with surgical complications and non-surgical complications. Log-rank test was used to determine statistical significance for the static calculation of 5-year survival and 3-year disease-free survival. The value of $p < 0.05$ was considered as statistically significant. We used Cox proportional hazards model to study the effect of independent factors on overall 5-year and 3-year disease-free survival. The SPSS Statistics package version 23.0 was used for statistical analysis.

RESULTS

The study included 550 patients. 165 (30%) patients have had surgical complications, 121 (22%) patients have had

non-surgical complications and 264 (48%) patients have had no complications. The clinical characteristics of patients are described in Table 1. Table 2 shows the type and prevalence of complication. According to clinical presentation degrees of anastomotic leakage is classified into grades (A, B or C). Grade A- anastomotic leakage eliminated without invasive intervention, grade B are those that are eliminated by invasive intervention other than repeated surgery (for example, percutaneous drainage), grade C are those that require repeated surgical intervention. The frequency of anastomotic leakage (B and C) was 14.5%; according to an X-ray examination (A), an extravasation of the contrast medium was detected in another 15.2% of cases. Thus, the total incidence of colorectal anastomosis leakage was 29.7%. The medical observation after surgery was 5 years 3 months (interquartile range 4.6–6.1 years).

Table 1: Clinical characteristics

Feature	No complications N= (%)	Surgical complications N = (%)	Non-surgical complications N= (%)	p
Gender				
Female	120 (45.4%)	72(43.6%)	53 (43.8%)	<0.05
Male	144 (54.5%)	93 (56.4%)	68 (56.2%)	
Age				
<65	79 (30%)	47 (28.7%)	27 (22%)	<0.05
66-75	135 (51%)	79 (47.9%)	60 (49%)	
>76	50 (19%)	39 (23.4%)	34 (28%)	
T stage				
T1-T2	63 (24%)	35 (21%)	23 (19%)	<0.05
T3	167 (63%)	109 (66%)	84 (70%)	
T4	34 (13%)	21 (13%)	14 (11%)	
N stage				
N0	168(64%)	104 (63%)	67 (55.3%)	>0.05
N1-2	96 (36%)	61 (37%)	54 (44.6%)	
Differentiation grade				
Low	232(87.8%)	107(64.8%)	91(75.2%)	<0.05
High	32 (12.1%)	58 (35.1%)	30 (24.7%)	
Cancer localization				
Ascending colon	113(42.8%)	71(43%)	53 (43.8%)	>0.05
Transverse colon	19(7.1%)	7 (4.2%)	20(16.5%)	
Descending colon	132 (50.1%)	87(52.8%)	48(39.7%)	
BMI (kg/m²)				
<18	1(0.3%)	1(0.6%)	14 (11.5%)	<0.05
18-25	213 (80.6%)	126 (76.3%)	95 (78.5%)	
>25	50(18.9%)	38 (23%)	12(9.9%)	

Concomitant morbidities	53 (20%)	28 (16.9%)	22 (18%)	>0.05
Data is presented in n (%) Chi ² test				
BMI-body mass index				

Table 2: Complications after surgery

Surgical complications	N= (%)
Anastomotic leakage	49 (29.7)
Ileus	39 (23.6)
Intra-abdominal infection	25 (15.1)
Sepsis	16 (9.7)
Bleeding	36 (21.9)
Non-surgical complications	N= (%)
Pneumonia	22 (18.1)
Electrolyte disorders	31 (25.7)
Delirium	18 (14.9)
Diarrhea	23 (19)
Malnutrition	16(13.3)
Constipation	11 (9)

The average age was 66.5 (range 19-82), 305 men (55.4%), 245 women (44.6%). In the groups with surgical and non-surgical complications, male sex, age over 65 years old, BMI higher 18 kg / m², stage of the tumor process T3, low grade was prevalent. There were no differences in the stages T1-2, N1-2, localization of the tumor process, concomitant pathology.

5-year OS by evaluable TNM classification in the current colon cancer research were analyzed depend on presence and absence postoperative complications. The proportion of patients with stage I was 23.8% in the group of patients without complications, 21.1% in the group of patients with surgical complications and 19.0% in the group with non-

surgical complications (log rank p<0.05). As presented in Figure 1 patients with stage I without postoperative complications have better 5- year OS, than those with similar stage in surgical and non-surgical complications groups. For patients with I stage in the group without complications, the 5- year OS was 88.9 %, which corresponds to published data (21). Average life expectancy for this group was 4.4 years and 4.8 years. As shown in the current analysis patients with surgical and non-surgical complications have worse survival rates, 60.0% and 65.2%, respectively. For this group, an adverse event (death) occurs between 2.3 years and 3.4 years, 3.2 years and 4 years, respectively (Fig.1).

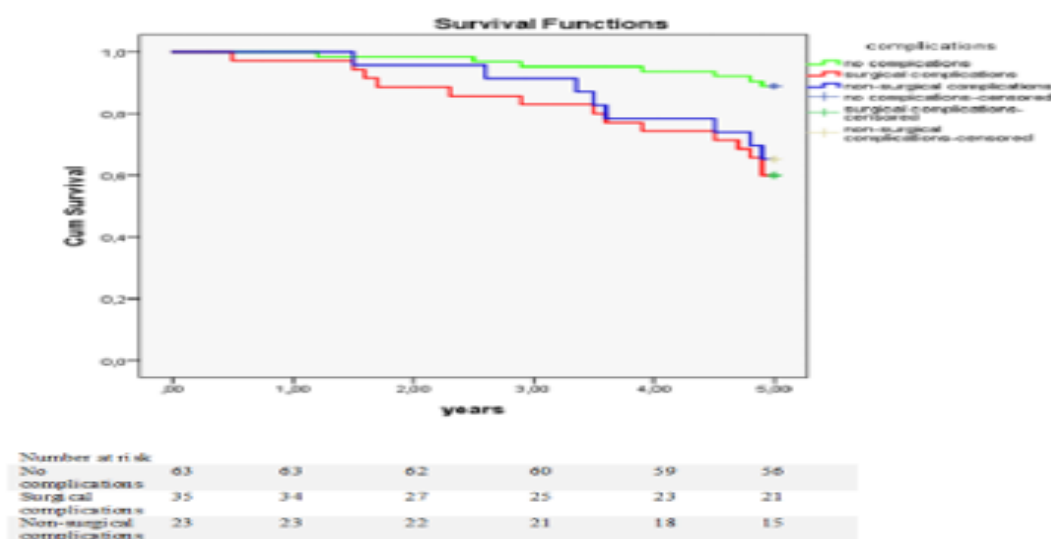


Figure 1: Kaplan-Meier survival curve for 5- year overall survival in patients with I stage colon cancer stratified by surgical, non-surgical complications and no complications.

3 year DFS for patients with colon cancer stage I had the following tendency: the survival rate for the group without complications was 88.9% with an average life expectancy of 2.9 to 3 years, for the group with surgical complications 60% and for the group with non-surgical

complications 65.5% with an average life expectancy of 2.0 to-2.7 years and 2.6 to 2.9 years respectively (p <0.05). So, 3-year DFS was worse in the complications group (p<0.05) (Fig.2).

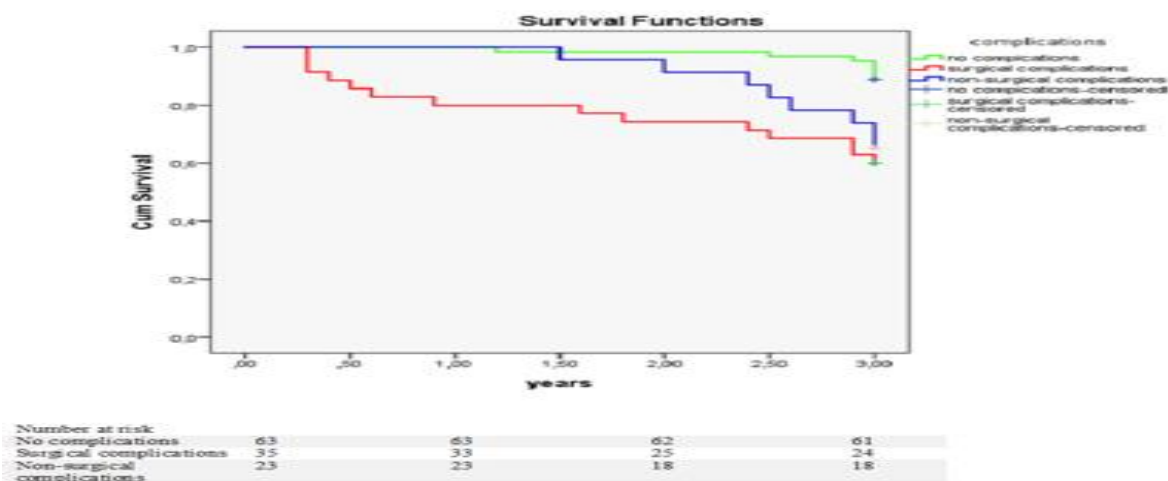


Figure 2: Kaplan-Meier survival curve for 3- year disease-free survival in patients with I stage colon cancer stratified by surgical, non-surgical complications and no complications.

Survival outcomes for patients with stage II are also illustrated in Figure 3. The percentage of patients with stage II of colon cancer in the group without complications was 45.4%, in the group of patients with surgical complications was 41.8% and in the group of patients with non-surgical complications was 36.3%. 5-year OS differences were also quite marked for patients' II stage without complications, surgical and non-surgical complications. According to the results of the study, with

95% certainty, we can say that the 5-year OS of patients without complications is 85%, where the average life expectancy is between 4.5 years and 4.8 years. For surgical complications group, 5-year OS was similar (60%) to that of patients with non-surgical complications (65%) (log rank $p < 0.05$). Average lifespan for both groups was 2.2 years and 3.9 years, 3.6 years and 4.5 years, respectively (Fig. 3).

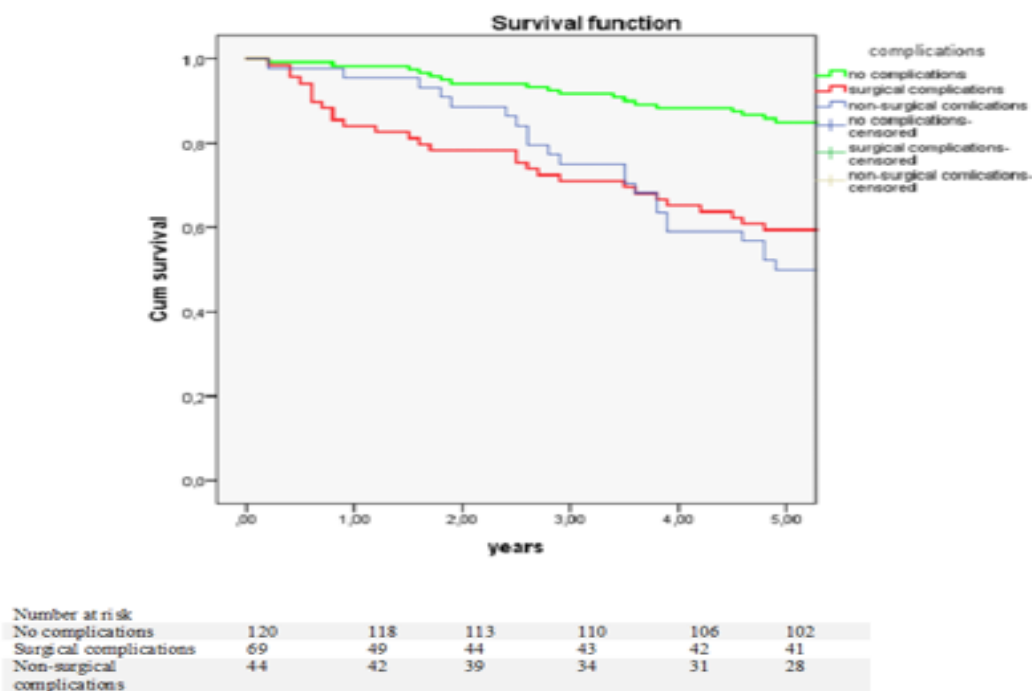


Figure 3: Kaplan-Meier survival curve for 5- year overall survival in patients with II stage colon cancer stratified by surgical, non-surgical complications and no complications.

For patients with stage II colon cancer, 3-DFS had the following tendency: for the group without complications, survival was 85% with an average life expectancy of 2.9 to 3 years, for the group with surgical complications 59.4%

and for the group with non-surgical complications 50% with the average life expectancy of 1.9 to 2.4 years, and 2.5 to 2.9 years, respectively (log rank $p < 0,05$) (Fig.4).

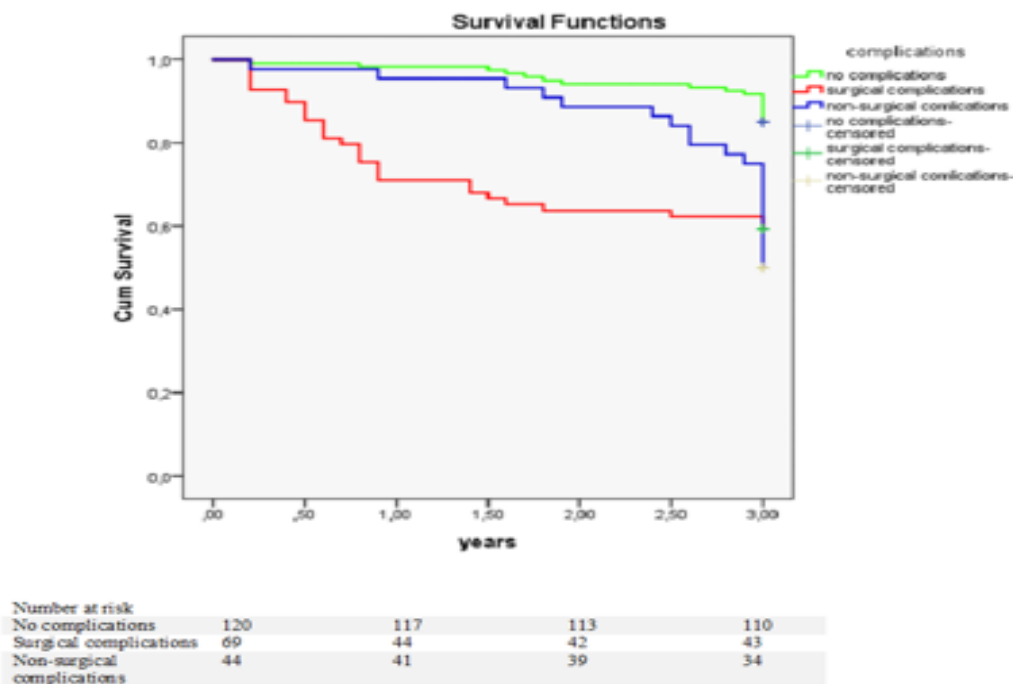


Figure 4: Kaplan-Meier survival curve for 3- year disease-free survival in patients with II stage colon cancer stratified by surgical, non-surgical complications and no complications.

5- year OS was calculated for III stage of colon cancer for three groups of patients. Actually, the number of patients without complications was 30.6%, with surgical complications 36.9%, with non-surgical complications 44.6% (Fig. 5). Patients without complications have better survival outcomes-81.5%. In contrast, of the 42.6% patients with surgical complications and 59.3% patients

with non-surgical complications have 5-year OS. Average life expectancy of patients without complications was 4.3 years and 4.7 years, of patients with surgical complications was 3 years and 3.8 years, of patients with non-surgical complications was 3.3 years and 4.3 years and (log rank $p < 0.05$).

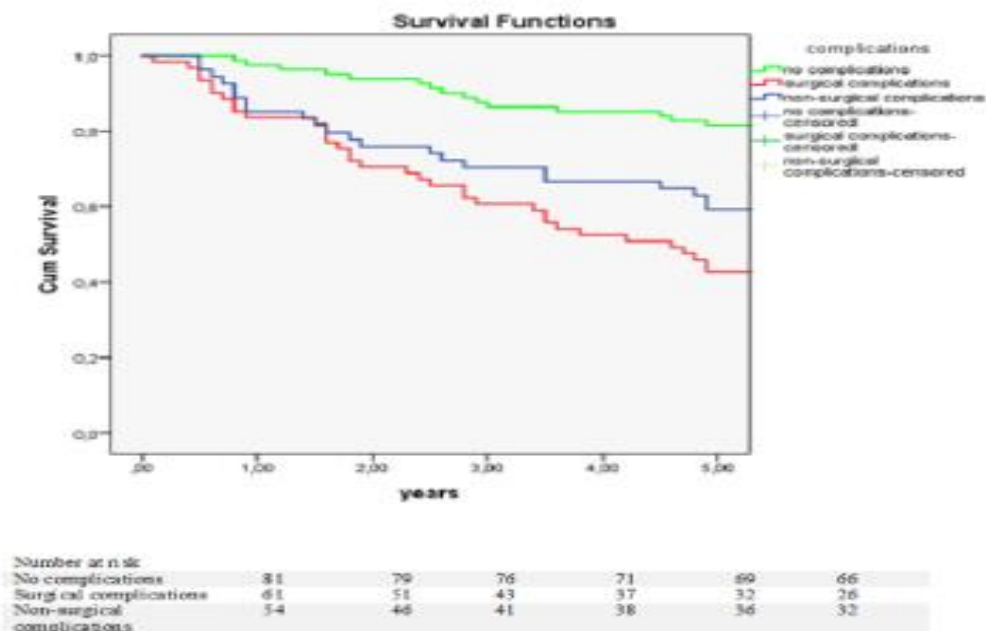


Figure 5: Kaplan-Meier survival curve for 5- year overall survival in patients with III stage colon cancer stratified by surgical, non-surgical complications and no complications.

3-year DFS for patients with stage III colon cancer had the following tendency: for the group without complications, the survival rate was 81.5% with an average life

expectancy of 2.7 to 2.9 years, for the group with surgical complications 42.6% and for the group with non-surgical complications 59.3% with an average life expectancy of 2.1

to 2.6 years and 2.2 to 2.7 years, respectively (log rank p <0.05) (Fig.6).

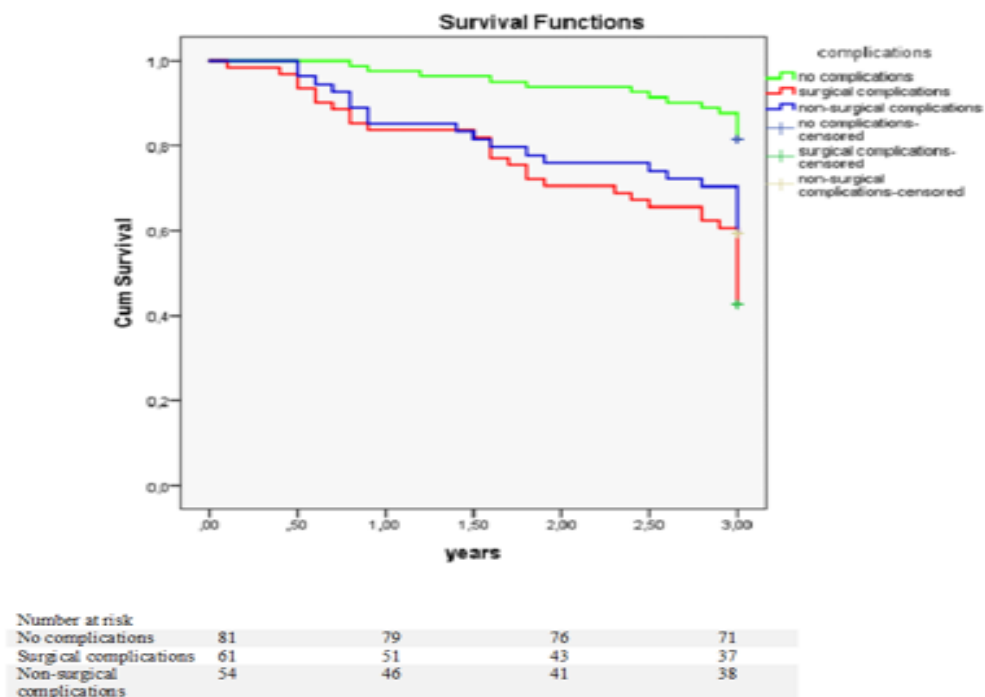


Figure 6: Kaplan-Meier survival curve for 3- year disease free survival in patients with III stage colon cancer stratified by surgical, non-surgical complications and no complications.

Cox regression models were used to assess risk factors that could affect the 5-year survival of patients. Age of 66-75 years (HR 1.75, 95% CI 1.35-2.20) and over 76 years old (HR 3.38, 95% CI 2.74-3.89), stage T3 (HR 1.35 95% CI 1.23-1.45) / T4 (HR 2.23, 95% CI 1.68-2.45, N 1-2 (HR 2.00, 95% CI 1.84-2.28), low grade of tumor (HR 1.47, 95% CI 1.32-1.68) negatively affects OS (Table 3). The surgical complications, such as anastomotic leakage grade B (HR 0.59, 95% CI 0.35-0.65), anastomotic leakage grade C (HR 3.36, 95% CI 1.83-5.91), bleeding (HR 1.96, 95% CI 1.05-3.85), sepsis (HR 4.10, 95% CI 2.15-7.89) reduced the 5-year life expectancy of patients. As well as patients with

non-surgical complications, such as electrolyte disorders (HR 2.28, 95% CI 0.15-3.58), diarrhea (HR 2.66, 95% CI 1.56-4.75), malnutrition (HR 1.90, 95% CI 1.20-2.89), had a shortened 5-year OS (Table 4). Surgical complications such as anastomotic leakage (grade C) (HR 1.87, 95% CI 0.60-2.42) and intra-abdominal infection (HR 1.87, 95% CI 1.11-2.35) had a negative effect on 3-year DFS. Among the non-surgical complication electrolyte disorders (HR 2.45, 95% CI 0.18-3.75), diarrhea (HR 2.75, 95% CI 0.89-2.99), malnutrition (HR 2.42, 95% CI 1.05-3.23), constipation (2.82, 95% CI 1.15-3.36) were a risk factors for 3-year DFS (Table 5)

Table 3: Cox univariate and multivariate regression analysis to evaluate risk factors associated with 5-year overall survival

Feature	Univariate Cox proportional hazard regression analysis			Multivariate Cox proportional hazard regression analysis		
	HR	CI 95%	p	HR	CI 95%	p
Gender						
Female	Reference			Reference		
Male	1.4	1.10-1.60	0.001	1.42	1.15-1.63	0.001
Age						
<65	0.25	0.10-0.38	0.8	0.36	0.12-0.41	0.041
66-75	1.86	0.45-2.31	0.02	1.75	1.35-2.20	0.010
>76	4.36	3.52-4.58	0.001	3.38	2.74-3.89	0.010
T stage						
T1-T2	0.29	0.22-1.15	0.041	0.15	0.10-0.25	0.08
T3	1.45	1.26-1.8	0.002	1.35	1.23-1.45	0.006
T4	2.65	2.25-3.05	0.001	2.23	1.68-2.45	0.001
N stage						

N0	Reference			Reference		
N1-2	1.86	1.62-1.96	0.004	2.00	1.84-2.28	0.001
Stage						
I	Reference			Reference		
II	2.57	2.35-2.84	0.07	1.91	1.50-2.14	0.006
III	4.26	3.48-5.26	0.028	2.95	2.24-3.75	0.002
Differentiation grade						
Low	1.52	1.35-1.68	0.001	1.47	1.32-1.68	0.001
High	Reference			Reference		
Cancer localization						
Ascending colon	0.25	0.10-0.38	0.6	0.29	0.15-0.42	0.8
Transverse colon	0.45	0.38-0.59	0.08	0.51	0.42-0.63	0.07
Descending colon	0.31	0.24-0.42	0.1	0.28	0.22-0.39	0.02
BMI (kg/m²)						
<18	Reference			Reference		
18-25	0.52	0.37-0.69	0.04	0.48	0.34-0.68	0.1
>25	0.42	0.30-0.54	0.028	0.44	0.28-0.59	0.3
HR- hazard ratio, CI- confidence interval						

Table 4: Cox univariate and multivariate regression analysis to evaluate complications associated with 5-year overall survival

Feature	Univariate Cox proportional hazard regression analysis			Multivariate Cox proportional hazard regression analysis		
	HR	CI 95%	p	HR	CI 95%	p
No complications	Reference			Reference		
Surgical complications						
Anastomotic leakage (grade A)	Reference			Reference		
Anastomotic leakage (grade B)	1.38	0.25-2.69	0.023	0.59	0.35-0.65	0.015
Anastomotic leakage (grade C)	3.38	1.92-5.93	0.001	3.36	1.83-5.91	0.001
Ileus	1.11	0.48-2.16	0.7	1.15	0.38-1.82	1.0
Intra-abdominal infection	0.28	0.05-1.93	0.2	1.11	0.47-2.85	0.2
Sepsis	6.65	3.58-12.82	0.001	4.10	2.15-7.89	0.001
Bleeding	2.58	1.38-4.75	0.003	1.96	1.05-3.85	0.04
Non-surgical complications						
Pneumonia	1.45	0.85-2.38	0.1	1.08	0.45-1.78	0.9
Electrolyte disorders	2.36	1.26-4.56	0.001	2.28	0.15-3.58	0.001
Delirium	1.39	0.68-2.96	0.8	1.18	0.45-2.88	0.028
Diarrhea	2.25	1.18-3.89	0.001	2.66	1.56-4.75	0.001
Malnutrition	3.00	1.94-4.66	0.001	1.90	1.20-2.89	0.006
Constipation	3.65	1.90-4.82	0.004	2.48	1.35-3.68	0.12
Comorbidities	2.82	1.63-4.89	0.4	2.04	1.08-3.87	0.7
HR- hazard ratio, CI- confidence interval						

Table 5: Cox univariate and multivariate regression analysis to evaluate complications associated with 3-year disease free survival

Feature	Univariate Cox proportional hazard regression analysis			Multivariate Cox proportional hazard regression analysis		
	HR	CI 95%	p	HR	CI 95%	p
No complications	Reference			Reference		
Surgical complications						
Anastomotic leakage (grade A)	Reference			Reference		
Anastomotic leakage (grade B)	1.49	0.56-2.35	0.036	1.25	0.58-1.89	0.018
Anastomotic leakage (grade C)	2.50	0.25-3.42	0.001	1.87	0.60-2.42	0.001
Ileus	0.25	0.12-1.65	0.9	0.65	0.22-1.28	1.0
Intra-abdominal infection	2.26	1.15-2.89	0.001	1.87	1.11-2.35	0.001
Sepsis	1.65	0.55-1.99	0.4	1.42	0.77-1.52	0.2
Bleeding	1.23	0.58-1.56	0.25	1.12	0.52-1.48	0.2
Non-surgical complications						
Pneumonia	1.45	0.85-2.38	0.1	1.08	0.45-1.78	0.9
Electrolyte disorders	2.36	1.26-4.56	0.001	2.28	0.15-3.58	0.001
Delirium	0.25	0.10-1.42	0.6	0.14	0.10-0.85	0.7
Diarrhea	3.58	1.5-4.62	0.001	2.88	1.45-3.72	0.001
Malnutrition	2.78	1.1-3.45	0.001	2.42	1.05-3.23	0.001
Constipation	3.22	1.45-4.02	0.001	2.82	1.15-3.36	0.001
Comorbidities	1.15	0.75-1.25	0.4	0.85	0.52-1.28	0.4
HR- hazard ratio, CI- confidence interval						

DISCUSSION

Surgery is the main treatment for colon cancer (4-9,22). Recently, studies have been conducted to study the effect of surgical operations on the life expectancy of patients (23-24). The study proves the relationship between survival and complications after radical surgical treatment of colon cancer.

The clinical characteristics of study participants is similar to other research about postoperative complications (9,22,24). We analyzed the overall survival of patients after radical surgical treatment of colon cancer, which were divided into three groups: patients without complications, patients with surgical complications and non-surgical complications. According to the results, there is a statistically significant difference between the survivals of patients in these groups. The survival of patients without complications is better than in patients with surgical and non-surgical complications. It can also be noted that patients with surgical complications have worse survival outcomes. According to previous studies, the survival rate of patients with stage I colon cancer is 90%, with stage II 84,7% -72,2%, with stage III 83,4% -44,3% (24). We received unexpected results, where the survival of patients is worse in the presence of surgical and non-surgical complications, despite the stage of cancer. Also, the impact on the survival of surgical and non-surgical complications was confirmed by Cox regression analysis. In the multivariate analysis surgical and non-

surgical complications were associated with older age, low differentiation grade, T and N stages, which are in line with other studies (25-26).

In this study surgical and non-surgical complications after colon cancer resection had similarly negative impact on 5-year overall survival and 3-year disease free survival. Among the surgical complication's anastomotic leakage (grade B and C), sepsis and bleeding reduced 5-year overall survival, whereas anastomotic leakage (grade B and C) and intraabdominal infection were potential factors to decrease 3-year disease free survival. In our study, anastomotic leakage is a more frequent complication than in previous studies. We compared our results with previous studies. The relationship of anastomotic leakage and worse tumor-specific survival was also demonstrated by Japanese surgeons (27). C. McArdle and *et al.* (28) confirmed the negative relationship between anastomotic leakage and overall and tumor-specific survival in the analysis treatment results for 2235 patients. J. Park *et al.* (29) when summarizing the treatment results, 10,477 patients found the worst relapse-free and overall survival after failure of the sutures anastomosis. O. Jannash *et al.* (30) noted the worst relapse-free survival in evaluating treatment outcomes in 17,867 patients. We concluded that surgical complications are a risk factor, leading to both deterioration in overall 5-year survival and a cause of recurrence of colon cancer. Although in most cases the mechanical method of anastomosis is used, we suggest

that a high incidence of anastomotic leakage may be associated with the method of the anastomosis.

Previous studies also demonstrate a relationship between complications after surgical operation and survival (14,26,37). A.J. Breugom *et al.* divided patients into groups with one, two and more complications. According to their research there were no differences between these groups in survival. The authors also show that anastomotic leakage, sepsis and blood loss significantly reduced both 1-year survival and 5-year overall survival. Other researchers investigated postoperative complications by Clavien -Dindo classification (17). So, in prospective analysis by Javier A. *et al.* major complications had worse influence on 5 and 10-year survival, however these complications did not reduce disease free survival. Similar investigation was conducted by Mrak *et al.* They reported that postoperative complications, categorization by Clavien-Dindo classification, did not show any significant impact on overall survival and disease free survival (17). On the contrary, J.M. Eberhardt *et al.* demonstrated significant reduction in disease free survival in patients with major complications.

We studied complications that are not an indirect association with colon resection. We called such complications non-surgical complications. There was pneumonia, electrolyte disorders, delirium, diarrhea, malnutrition and constipation. In the current study, it was demonstrated that non-surgical complications such as electrolyte disorders, diarrhea and malnutrition reduced overall survival. Furthermore, diarrhea and malnutrition had a significant negative impact on the 3-year disease free survival. The result of this study regarding electrolyte disorders coincides with the previous study, where electrolyte disorders reduced 5-year survival (16). In previous studies delirium was associated with worse 5-year overall survival (16) also with prolonged hospitalization and unsatisfactory rehabilitation (32). However, in this study we did not find the significant impact of delirium on survival. A noticeable finding of our research was influence of non-surgical complications such as diarrhea and malnutrition on 5-year overall survival, while diarrhea, malnutrition and constipation had great negative impact on 3-year disease free survival.

This study has limitations. Firstly, this study was a retrospective. Single-center research with relatively small sample size. Secondly, the study included complications that were reported in the first month after surgery. The main strength of this study is detailed review of each complication depending on the direct and indirect effect of the surgical treatment of colon cancer.

Conclusion. Surgical and non-surgical complications had a negative impact on 5-year overall survival and 3-year disease free survival.

CONFLICT OF INTEREST

No conflict of interest

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