

Analysis of Prognostic Factors in Complicated Colorectal Cancer Operated in Emergency

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Rezumat

Analiza factorilor prognostici în cancerul colorectal complicat operat în urgență

Introducere: În anul 2018 cancerul de colon se afla pe locul al 5-lea ca mortalitate prin cancer, iar cancerul rectal pe locul al 10-lea. Supraviețuirea la distanță a bolnavilor cu cancer colorectal operat în urgență, rămâne nesatisfăcătoare, decesul fiind datorat recidivelor locale și a metastazelor.

Scopul: Evaluarea unor corelații ale supraviețuirii globale cu caracteristici clinico-paraclinice, tumorale sau de tratament pentru identificarea factorilor de prognostic la pacienții cu cancer colorectal operat în urgență.

Material și Metode: Am efectuat o analiză retrospectivă la 431 pacienți cu cancer colorectal operat în urgență în perioada 2008-2017, cu excluderea celor 40 de pacienți cu decese postoperatorii, cu o perioadă de urmărire de cel puțin un an. S-au efectuat corelații ale unor caracteristici clinico-paraclinice, tumorale sau de tratament cu supraviețuirea globală.

Rezultate: În analiza statistic univariată de supraviețuire, se obține o asociere semnificativă statistic cu: vârsta > 61 ani (p_value = 0,000049), antecedentele chirurgicale abdominal (p_value = 0,031725), bolile cardiace (p_value = 0,000007), fibrilația atrială (p_value = 0,007496), diagnosticul la internare (p_value = 0,034352), cașexia (p_value = 0,000000), oligoanuria (p_value = 0,000000), anemia (p_value = 0,000006) dezechilibrul hidro-electrolitic (p_value = 0,000001), localizarea tumorală (p_value =

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0,000030), invazia în organele vecine (p_value = 0,000000), aspectul de pelvis înghețat (p_value = 0,000000), carcinomatoza peritoneală (p_value = 0,000000), metastazele hepatice (p_value=0,000000), tipul de intervenție chirurgicală (p_value = 0,000000), limfodisecția (p_value = 0,000001), biopsia hepatică (p_value = 0,043483), reintegrarea tranzitului intestinal (p_value = 0,000000), intervențiile seriate (p_value = 0,000000), pTNM (p_value = 0,000000), gradingul (p_value = 0,007069). Analiza de regresie multivariată Cox a arătat că: vârsta > 61 ani - HR=1.026, 95%CI(1.012, 1.039) (p_value = 0.000139), cașexia - HR = 1.358, 95%CI(1.046, 1.764) (p_value = 0,021617), carcinomatoza peritoneală - HR = 2.346, 95%CI(1.163, 4.732) (p_value = 0,017253), stadiul bolii - HR=36.745, 95%CI = (14.778, 91.366) (p_value = 0,000000), tipul de intervenție - HR = 0.187, 95%CI(0.045, 0.779) (p_value = 0,021281) și intervențiile seriate - HR = 0.282, 95%CI(0.144,0.551) (p_value = 0,000213) sunt factori de prognostic independenți.

Concluzii: Factorii de prognostic pentru bolnavii cu cancere colorectale operate în urgență sunt: vârsta > 61 ani, prezența antecedentelor chirurgicale abdominale și a tarelor cardiace asociate, în special a fibrilației atriale, diagnosticul de iminență de perforație diastatică, cașexia, oligoanuria, anemia și dezechilibrul hidro-electrolitic prezente la internare, tumorile rectale, invazia tumorală în organe vecine, aspectul de “pelvis înghețat”, prezența metastazelor hepatice sau a carcinomatozei peritoneale, tumorile nediferențiate, stadiul III sau IV, practicarea unei derivații interne sau neefectuarea limfodisecției. Vârsta peste 61 de ani, cașexia, precum și carcinomatoza peritoneală sunt factori de risc independenți, iar, operația Hartmann și intervențiile seriate sunt factori de protecție independenți.

Cuvinte cheie: cancer colorectal, factori de pronostic, urgență, tratament chirurgical

Abstract

Introduction: In 2018, the colon cancer was the 5th type of neoplasia regarding the cancer mortality and the rectal cancer was the 10th. The survival of patients with colorectal cancer operated in emergency still remains unsatisfactory, the death being due to local recurrences and to metastases. The aim of this study is to evaluate some correlations of overall survival with clinic and paraclinic features, tumor or treatment characteristics in order to identify prognostic factors, for cases with colorectal tumors that underwent emergency surgery.

Material and Methods: We performed a retrospective analysis on 431 patients with colorectal cancer operated in emergency between 2008-2017, excluding 40 patients with postoperative deaths, with a follow-up period of at least one year. There were correlations of some clinic and paraclinic features, tumor or treatment characteristics with the overall survival.

Results: In the univariate statistical survival analysis, a statistically significant association was obtained with: the age > 61 years (p_value = 0.000049), abdominal surgical history (p_value = 0.031725), heart disease (p_value = 0.000007), atrial fibrillation (p_value = 0.007496), preoperative diagnosis (p_value = 0.034352), cachexia (p_value = 0.000000), oliguria (p_value = 0.000000), anemia (p_value = 0.000006) hydro-electrolytic disorders (p_value = 0.000001), tumor localization (p_value = 0.000030), invasion into other organs (p_value = 0.000000), appearance of “frozen pelvis” (p_value = 0.000000), peritoneal carcinomatosis (p_value = 0.000000), liver metastases (p_value = 0.000000), type of surgery (p_value = 0.000000), lymph node dissection (p_value = 0.000001), liver biopsy (p_value = 0.043483), stoma reversal (p_value = 0.000000), serial interventions (p_value = 0.000000), pTNM (p_value = 0.000000), tumor grading (p_value = 0.007069). The Cox multivariate regression analysis revealed that: the age > 61 years - HR = 1,026, 95% CI (1,012, 1,039) (p value = 0.000139), cachexia - HR = 1,358, 95% CI (1,046, 1,764) (p value = 0.021617), peritoneal carcinomatosis - HR = 2.346, 95% CI (1.163, 4.732) (p_value = 0.017253), disease stage - HR = 36.745, 95% CI (14.778, 91.366) (p_value = 0.000000), intervention type - HR = 0.187, 95% CI (0.045, 0.779)

(p_value = 0.021281) and serial interventions - HR = 0.282, 95% CI (0.144-0.551) (p_value = 0.00213) are independent prognostic factors.

Conclusions: The prognostic factors for patients with colorectal cancers operated in emergency are: the age > 61, the presence of abdominal surgical history and associated cardiac conditions, especially atrial fibrillation, diagnosis of diastatic perforation imminence, cachexia, oliguria, hydro-electrolytic disorders at admission, rectal tumors, tumor invasion in other organs, the appearance of "frozen pelvis", the presence of liver metastases or peritoneal carcinomatosis, undifferentiated tumors, stage IV, practicing an internal derivation or not performing lymph node dissection. The age over 61, cachexia, as well as peritoneal carcinomatosis, stage III or IV are independent risk factors the Hartmann procedure and the serial interventions are independent protective factors.

Key words: colorectal cancer, prognostic factors, emergency, surgical treatment

Introduction

According to GLOBOCAN data, in 2012 there were 1.36 million newly diagnosed cases and 700,000 deaths caused by colorectal cancer (1). The recent GLOBOCAN 2018 analysis ranks the colon cancer in the 5th place as cancer mortality, with 551,000 deaths and the rectal cancer in the 10th place, with 300,000 deaths (2).

Although many therapeutic strategies have been developed in the last decades, the long-term survival of patients with colorectal cancer, especially those admitted in emergency with complicated tumors, remains unsatisfactory, due to local recurrences and metastases (3). According to the recent EURO CARE 5 analysis, the colorectal cancer had a minimal increase in 5-years survival over time (4).

In the emergency surgery conditions, it is considered that only about half of the patients can benefit from gestures with curative intent, the morbidity and the mortality in these cases being evidently higher compared to the elective interventions. Even when performing surgery with curative intent, the 5-year survival of these patients rarely exceeds 30% (5).

The factors that influence the survival of patients with colorectal cancer, operated in emergency, are: age, biological status upon admission, symptomatology, tumor localiza-

tion, invasion in other organs, presence of secondary disseminations, type of surgical intervention, need for re-interventions, complications after surgery, histological type, tumor grading and staging (6,7).

In a 2012 guide from the European Society of Medical Oncology, the colorectal cancer occlusion and perforation are mentioned as being associated with poor prognosis and short-term survival in association with primary T4 tumors, incomplete lymph node dissection, invasion of lymphatic vessels and perineural invasion (8).

The 5-years survival of patients with colorectal cancer in advanced stages was evaluated for elective operations: for stage II- 87% - 50%, for stage III- 85-13% and for stage IV-12% (9-11). The overall survival at 5 years for colorectal cancer patients operated in emergency has been evaluated in few studies and it is around 39% (12).

Patients and Methods

We retrospectively analyzed the data of 431 patients admitted and operated for complicated colorectal cancers in the Surgery II clinic of the "Sf. Ap. Andrei" from Galati, between 2008-2017. For this study, we excluded the 40 post-operative deaths, leaving a group of 391 patients, for whom we performed the survival analysis. There were followed both the post-operative evolution and the re-admissions in

the case of those with serial interventions, the controls of those operated during 2012-2017 and the number of survivors using the patient identification data in the Hipocrate/SIUI medical information system.

As prognostic factors of complicated colorectal cancer, epidemiological, clinico-para-clinical, therapeutic and tumor factors were analyzed. The following epidemiological and clinical factors were analyzed: age, sex, area, abdominal surgical history, comorbidities, preoperative diagnosis. We analyzed the following paraclinical factors: the values of hemoglobin, hematocrit, leukocytes, platelets and ionograms at admission. Among the therapeutic factors, we analyzed: tumor localization, invasion into other organs, intraoperative appearance of "frozen pelvis", presence of hepatic metastases and peritoneal carcinomatosis, type of surgery performed in emergency, lymphodissection, liver biopsy, stoma reversal of Hartmann procedures. The tumor factors analyzed were: pTNM stage, tumor grading and presence of mucus component.

Study Design

The patients included in this study were those with long-term survival, retrospectively analyzed. Epidemiological, clinic, pathologic, therapeutic and tumor characteristics were evaluated in the survival analysis.

Statistical Analysis

The survival analysis was performed from the time of diagnosis to the time of patients' death or until stopping the follow-up in the study (01.10.2019). As prognostic factors, survival curves were analyzed, using Kaplan-Meier method and the statistical significance analysis was performed with Log Rank (Mantel-Cox) and Breslow (Generalized Wilcoxon) tests. The mean and median survival time were calculated for survival estimation at 6, 12, 18, 24, 48 and 60 months.

To identify potential prognostic factors, survival curves were analyzed, using the

Kaplan-Meier method, and statistical significance analysis was performed with Log Rank (Mantel-Cox) and Breslow (Generalized Wilcoxon) tests. Survival and median survival were calculated and survival was estimated at 6, 12, 18, 24, 48 and 60 months. For the verification of the obtained results, the analysis of the proportional risk ratio Univariate Cox (HR) was performed, and for the statistical significance comparison we used the sig-p-value test with 95.0% CI. The analysis of the Cox multivariate proportional risk ratio (HR) was performed to evaluate potential independent prognostic factors by introducing only those statistically significant variables detected in the univariate analysis. The accuracy of the prognostic factors was analyzed by evaluating the sensitivity and specificity of these markers, after establishing the cut off values, using the ROC curves.

Statistical analysis was performed using SPSS software (version 23.0). Statistical conclusions were formulated using as a statistically significant difference value $p < 0.05$ for all calculations performed.

Results

Until the end of this study (01.10.2019), there were 379 (87.93%) deaths and 12 survivors (2.79%). The average survival was 19.81 months and the 5-year survival was 3.1%.

We couldn't identify statistical relevance for survival in terms of the involvement of epidemiological factors: sex ($p_{\text{value}} = 0.348363$), provenance environment ($p_{\text{value}} = 0.465583$), hereditary-collateral antecedents ($p_{\text{value}} = 0.857916$), colic resections antecedents ($p_{\text{value}} = 0.186804$), liver cirrhosis ($p_{\text{value}} = 0.106936$), pre-existing colon pathology ($p_{\text{value}} = 0.571957$), clinic and paraclinic factors: presence of abdominal pain at admission ($p_{\text{value}} = 0.748323$), presence of intestinal transit disorders ($p_{\text{value}} = 0.834845$), severe anemia with preoperative transfusion ($p_{\text{value}} = 0.921275$), leukocytosis ($p_{\text{value}} = 0.099868$), thrombocytopenia ($p_{\text{value}} = 0.106936$), operative factors: type of parietoraphy ($p_{\text{value}} = 0.103058$), postoperative complications (p_{value}

= 0.774076), reoperations ($p_{\text{value}} = 0.768389$), tumor factors: pathological type ($p_{\text{value}} = 0.172264$), presence of tumors with mucus component ($p_{\text{value}} = 0, 270 325$).

Comparing the survival in patients who had increased values of the age with those who had low values of age, the risk of death was calculated in the case of the presence of increased values of the age - HR = 1,032, 95% CI = (1,022,01,043) ($p_{\text{value}} = 0.000000$) - the presence of increased age values is a risk factor.

The ROC curve was constructed for age in the discrimination of death in the 391 patients involved in the study, of which 379 died (96.93%) and 12 survivors (3.07%). It has an area of 0.764, with 95% CI of (0.718 to 0.805), $p_{\text{value}} = <0.0001$. The cutoff point is > 61 , with a sensitivity of 68.9 and a specificity of 75.00 (*Fig. 1*).

The mean survival time in patients with cutoff value for age ≤ 61 was 24,376, 95% CI = (21,470, 27,282) and in those with cutoff > 61 was 17,646, 95% CI = (16,010, 19,282), the difference between survival time in patients with values above cutoff and below cutoff being statistically significant ($p_{\text{value}} = 0.000049$) (*Table 1, Fig. 2*).

Of the 150 patients with abdominal surgery history, 147 died and 3 (2%) survived until 01.10.2019. Of the 241 patients without abdominal surgery history, 232 died and 9 (3.7%) survived until the end of the study. Comparing the survival on the 2 groups, a statistically significant difference is observed ($p_{\text{value}} = 0.031725$).

The mortality risk for patients past surgical history (abdominal) was - HR = 1.116, 95% CI (1.006.1.238) ($p_{\text{value}} = 0.038236$). The 5-year survival rate of those patients is 1.5% and for those without abdominal surgical history, the 5-year survival is 1.7% (*Table 1*).

Of the 121 patients with heart disease, 119 died by 01.10.2019 and 2 (1.7%) survived. Of the 270 patients without associated cardiac diseases, 260 died, and 10 (3.7%) were alive at the end of the study. Comparing the survival on the 2 groups, there is a statistically significant difference ($p_{\text{value}}=0, 000007$).

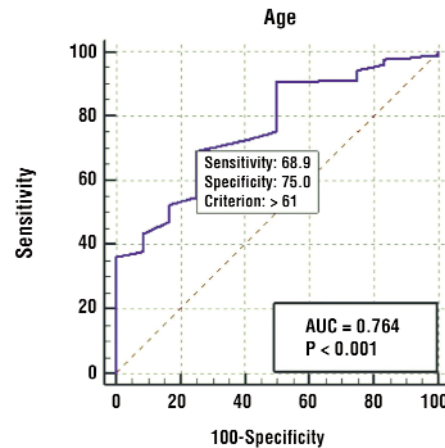


Figure 1. ROC curve for age

The mortality risk in cases with associated cardiac disease was - HR = 1.247, 95% CI (1.141.1,422) ($p_{\text{value}} = 0.000016$). In this cases the 5-years survival is 0%, while in the patients without cardiac disease, the 5-year survival is 2.4% (*Table 1*).

Of the 27 patients with permanent atrial fibrillation history, none survived until 01.10.2019. Of the 364 without atrial fibrillation, 352 died and 12 (3.3%) survived. Comparing the survival on the 2 groups, there is a statistically significant difference ($p_{\text{value}} = 0.007496$).

The risk of death in cases that presented with atrial fibrillation was - HR = 1.293, 95%

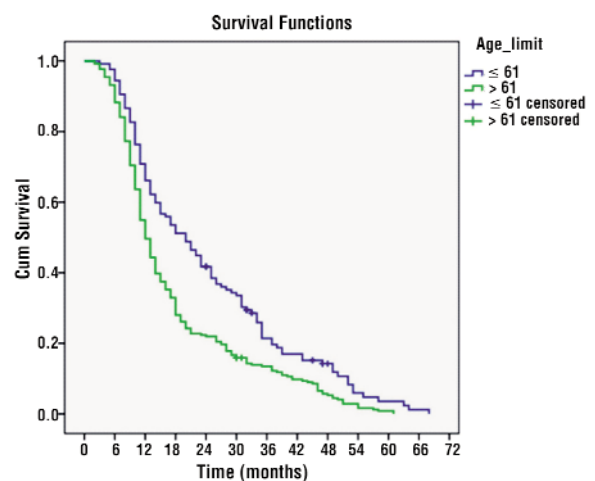


Figure 2. Survival curves for age variable with cut-off value (C)

Table 1. Survival analysis of prognostic factors – u- univariate, m- multivariate, ref- reference

Prognostic factor	Deaths	Mean Estimate	Median Estimate	5-y survival rate (%)	p_value (Log Rank (Mantel-Cox))	Univariate		Multivariate	
						HR (95%CI)	p_value	HR (95%CI)	p_value
Age									
<61	118/127	24.376	20.000		0.000049	1.032	0.000000	1.026	0.000139
>61=ref	261/264	17.646	12.000			(1.022, 1.043)		(1.012, 1.039)	
Sex									
F	153/159				0.348363		0.364690		
M	226/232								
Provenience area									
R	146/152				0.465583		0.480728		
U	233/239								
HCA									
YES	38/38				0,857916		0.862515		
NO	341/353								
Surgical abdominal history									
YES	147/150	17.931	11.000	1.5%	0,031725	1.116	0.038236		
NO	232/241	20.989	15.000	1.7%		(1.006, 1.238)			
Colonic resections antec.									
YES	374/386				0,186804		0.207577		
NO	379/391								
Cardiac diseases									
YES	119/121	15.464	11.000	Max 54	0,000007	1.274	0.000016		
NO	260/270	21.766	16.000	2.4%		(1.141, 1.422)			
Atrial fibrillation									
YES	27/27	13.889	10.000	Max 49	0,007496	1.293	0.010431		
NO	352/364	20.260	14.000	1.8%		(1.062, 1.574)			
Cirrhosis									
YES	6/6				0,106936		0.125853		
NO	373/385								
Bowel pathology									
YES	16/16				0,571957		0.125853		
NO	363/375								
Abdo pain									
YES	336/346				0,748323		0.756490		
NO	43/45								
Bowel habit disturb									
Yes	333/343				0,834845		0.840303		
No	46/47								
Pre op Dg									
H	41/43	20.579	14.000	3.6%	0.034352				
I	12/12	11.333	9.000	Max 51					
O	305/314	20.248	14.000	1.5%		1.750 (1.118, 2.738)	0.014287		
P=Ref	21/22	16.818	12.000	Max 52		.800 (.647, .990)	0.0398		
Cachexia									
Yes	95/98	13.875	10.000	Max 51	0,000000	1.371	0.000000	1.358	0.021617
No	284/293	21.814	16.000	2.1%		(1.218, 1.543)		(1.046, 1.764)	
anuria									
Yes	88/88	11.455	10.000	Max 48	0,000000	1.585	0.000000		
No	291/303	22.249	16.000	2.1%		(1.400, 1.796)			
Anemia									
Yes	251/260	17.124	12.000	1.2%	0,000006	1.272	0.000015		
No	128/131	25.151	18.000	2.5%		(1.141, 1.418)			
Transfusion									
Yes	79/81				0,921275		0.923898		
No	300/310								
High WBC									
Yes	45/46				0,099868		0.112409		
No	334/345								
Low PLT									
Yes	6/6				0,106936		0.125853		
No	373/385								
Electrolite disturbance									
Yes	138/139	15.061	11.000	0.8%	0,000001	1.291	0.000002		
No	241/252	22.435	16.000	2.1%		(1.1611.435)			

Prognostic factor	Deaths	Mean Estimate	Median Estimate	5-y survival rate (%)	p_value (Log Rank (Mantel-Cox))	Univariate		Multivariate	
						HR (95%CI)	p_value	HR (95%CI)	p_value
Tum location									
Ascend	54/55	23.590	20.000	1.9%	0.000030				
Descend	52/54	16.706	12.000	Max 47					
Rect	135/136	15.327	11.000	1.7%					
Sigmoid	113/120	24.284	18.000	2.1%		1.348 (1.125, 1.614)	0.001207		
Transvers=Ref	25/26	20.269	13.000	Max 50		.757 (.627, .913)	0.003560		
Vicinity invasion									
Yes	107/107	9.449	9.000	Max 35	0,000000	2.110(1.857, 2.398)	0.000000		
No	272/284	23.725	18.000	2.2%					
Frozen Pelvis									
Yes	34/34	7.000	7.000	Max13	0,000000	2.745 (2.254, 3.344)	0.000000		
No	345/357	21.036	15.000	1.8%					
Carcinomatosis									
Yes	10/10	6.600	6.000	Max 10	0,000000	2.631 (1.897, 3.648)	0.000000	2.346	0.017253
No	369/381	20.162	14.000	1.7%				(1.163, 4.732)	
LIVER mets									
Yes	68/68	8.515	8.000	Max 41	0,000000	2.271(1.959, 2.633)	0.000000		
No	311/323	22.196	17.000	2.0%					
Operation									
1	154/155	14.010	10.000	1.5%	0.000000	2.405 (1.827, 3.166)	0.000000	.187(.045, .779)	0.021281
2	117/124	24.177	18.000	2.2%					
3=ref(m)	27/27	8.222	8.000	Max 13					
4=ref(u)	81/85	27.585	23.000	1.5%					
Nodes excision									
Yes	72/76	29.226	25.000	1.6%	0,000001	.737 (.648, .839)	0.000004		
No	307/315	17.544	12.000	1.2%					
Liver biopsy									
Yes	13/14	14.143	10.000	Max 41	0,043483	1.316 (.996, 1.738)	0.053414		
No	366/377	20.029	14.000	1.7%					
Primary closure									
Yes	373/383				0,103058		0.120910		
No	6/6								
Pulmonary compl									
Yes	45/45				0,774076		0.781227		
No	334/346								
Redo laparotomy									
Yes	21/22				0,768389		0.776511		
No	358/369								
Colostomy reversal									
Yes	49/57	39.156	35.000	4.9%	0,000000	.175 (.124, .247)	0.000000		
No	201/201	10.965	11.000	Max 28					
Multiple surgeries									
Yes	72/80	37.437	35.000	6.4%	0,000000	.216 (.167, .279)	0.000000	.282(.144, .551)	0.000213
No	228/228	10.640	10.000	Max 28					
pTNM									
2=ref	10/96	40.415	39.000	5.9%	0,000000	25.482 (15.585, 41.663)	0.000000	11.114 (4.835, 25.595)	0.000000
3	214/216	13.348	12.000	Max 30					
4	69/69	8.029	8.000	Max 13					
Pathology									
ADK	378/390				0,172264		0.212241		
GIST	1/1								
Grading									
1=ref	101/106	21.397	14.000	1.4%	0.007069	1.814 (1.224, 2.689)	0.003003		
2	244/251	20.026	14.000	1.9%					
3	34/34	13.353	11.000	Max 53					
Mucinous type									
Yes	16/16				0.270325		0.288271		
No	363/375								

CI (1.0621.1.574) (p value = 0.010431). We found that the 5-year survival of cases with atrial fibrillation is 0%, while in patients without atrial fibrillation, the 5-year survival is 1.8% (Table 1).

Of the 43 patients with hemorrhagic tumors at admission, 41 died by the end of the study and 2 (4.7%) survived. Of the 12 patients who presented with diastatic perforation imminence, none were alive at the end of the study. Of the 314 patients with intestinal occlusions /subocclusions, 305 died and 9 (2.9%) survived until the end of the study. Of the 22 patients with intestinal perforation, 21 died and one (4.5%) survived by the end of the study. Comparing the survival on the 4 groups, there is a statistically significant difference (p _value = 0.034352), more precisely, significant differences between patients with hemorrhage and those with imminent diastatic perforation (p -value = 0.011984) and between those with imminence of diastatic perforation and those with intestinal occlusion (p -value = 0.006827) (Fig. 3).

The risk of death for patients operated for the imminent diastatic perforation was - HR = 1,750, 95% CI (1,118,2.738) (p _value = 0.014287), and of those with occlusion - HR = 0.800, 95% CI (0.647.0.990) (p _value = 0.039869), compared with those with perforated tumors. The 5-years survival of patients with hemorrhage at

admission is 3.6%, while in patients with imminent diastatic perforation it is 0%. For patients with intestinal occlusion at admission, the 5-years survival is 1.5% and for those with intestinal perforation it is 0% (Table 1).

Of the 98 patients who presented with cachexia at admission, 95 died and 3 (3.1%) survived until 01.10.2019. Of the 293 patients without cachexia, 284 died and 9 (3.1%) were alive at the end of the study. Comparing the survival on the 2 groups, there is a statistically significant difference (p _value = 0.000000).

The risk of death in patients with casexia was -HR = 1.371, 95% CI (1.218.1.543) (p value = 0.000000). The 5-year survival of patients with cachexia is 0%, while in those without cachexia, the 5-year survival is 2.1% (Table 1).

Of the 88 patients with oliguria at admission, none survived until 01.10.2019. Of the 303 patients with normal diuresis, 291 died and 12 (4.0%) were alive by the end of the study. Comparing the survival on the 2 groups, there is a statistically significant difference (p _value = 0.000000).

Death risk for oliguric patient was - HR = 1.585, 95% CI (1.400.1.796) (p value = 0.000000). The 5-years survival of patients with oliguria is 0%, while in patients without oliguria, the 5-years survival is 2.1% (Table 1).

Of the 260 patients admitted with anemia, 251 died and 9 (3.5%) survived until 01.10.2019. Of the 131 patients without anemia at admission, 128 died and 3 (2.3%) were alive by the end of the study. Comparing the survival on the 2 groups, there is a statistically significant difference (p _value = 0.000006). The mortality risk for patients with oliguria was - HR = 1.585, 95% CI(1.400.1.796) (p _value 0.000000). The 5-years survival of patients with anemia at admission is 1.2%, while for patients without anemia, the 5-year survival is 2.5% (Table 1).

Of the 139 patients with hydro-electrolytic disorders at admission, 138 died and one survived until 01.10.2019. Of the 252 patients without hydro-electrolyte disorders, 241 died and 11 (4.4%) were alive by the end of the study. Comparing the survival on the 2 groups, a statistically significant difference is

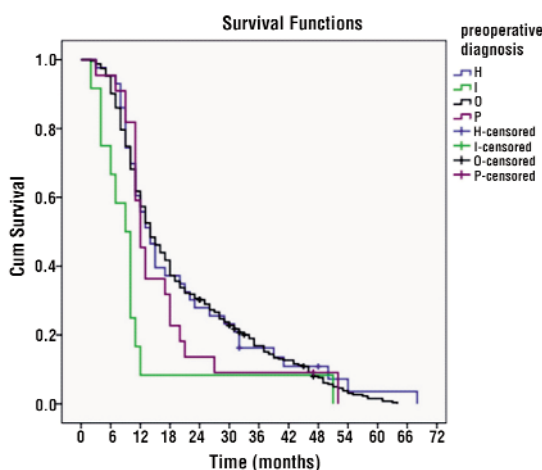


Figure 3. Survival curves Kaplan Meier according to the preoperative diagnosis

obtained ($p_value = 0.000001$). For patients with electrolyte imbalance the risk of death was - $HR = 1.291$, 95% CI (1.161,1,435) ($p_value = 0.000002$). The 5-years survival of patients with hydro-electrolyte disorders at admission is 0.8%, while for patients without hydro-electrolyte disorders, the 5-years survival is 2.1% (*Table 1*).

Of the 55 patients with tumors in right colon, 54 died by the end of the study and one (1.8%) survived. Of the 26 patients with transverse colon tumors, 25 died and 1 (3.8%) was alive at the end of the study. Of the 54 patients with descending colon tumors, 52 died and 2 (3.7%) survived until the end of the study. Of the 120 patients with sigmoid colon tumors and recto-sigmoid junction, 113 died and 7 (5.8%) were alive at the end of the study. Of the 136 patients with rectal tumors, 135 died and 1 (0.7%) survived by the end of the study. Comparing the survival on the 5 groups, a statistically significant difference ($p_value = 0.000030$) is obtained, more precisely, there are statistically significant differences between the locations on the ascendant and descendant colon ($p_value = 0.018036$), between the locations on the ascendant colon and the rectum ($p_value = 0.003738$), between the locations on the descendant and on the sigmoid ($p_value = 0.000819$) and between the locations on the rectum and the sigmoid ($p_value = 0.000003$) (*Fig. 4*).

The risk of death in patients operated for rectal tumors was - $HR = 1.348$, 95% CI (1.125, 1.614) ($p_value = 0.001207$), and of those with sigmoid tumors - $HR = 0.757$, 95% CI (0.627, 0.913) ($p_value = 0.003560$), compared with those with transverse tumors. The 5-years survival of patients with ceco-ascendant tumors is 1.9%, while in patients with descendant tumors, the 5-years survival is 0%. For patients with rectal tumors, the 5-year survival is 1.7%, for those with sigmoid tumors 2,1%, and for those with transverse colon tumors 0% (*Table 1*).

Of the 107 patients with tumor invasion in other organs, none survived until 01.10.2019. Of the 284 patients without tumor invasion in

other organs, 272 died and 12 (4.2%) were alive at the end of the study. Comparing the survival on the 2 groups, there is a statistically significant difference ($p_value = 0.000000$).

The risk of death for patients with tumor invasion in the neighboring organs was - $HR = 2.110$, 95% CI (1.857, 2.398) ($p_value = 0.000000$). The 5-years survival of patients with invasive tumors in other organs is 0% and in patients with non-invasive tumors, the 5-years survival is 2.2% (*Table 1*).

Of the 34 patients with "frozen pelvis", none survived until 01.10.2019. Of the 357 patients without "frozen pelvis", 345 died and 12 (3.4%) were alive at the end of the study. Comparing the survival on the 2 groups, there is a statistically significant difference ($p_value = 0.000000$).

The risk of death in patients with frozen pelvis was - $HR = 2.2745$, 95% CI (2.254,3.344) ($p_value = 0.000000$). The 5-years survival of patients with "frozen pelvis" is 0%, while in patients without "frozen pelvis", the 5-year survival is 1.8% (*Table 1*).

Of the 10 patients with peritoneal carcinomatosis, none survived until 01.10.2019. Of the 381 patients without peritoneal carcinomatosis, 369 died and 12 (3.1%) were alive at the end of the study. Comparing the survival on the 2 groups, we found a statistically significant difference ($p_value = 0.000000$).

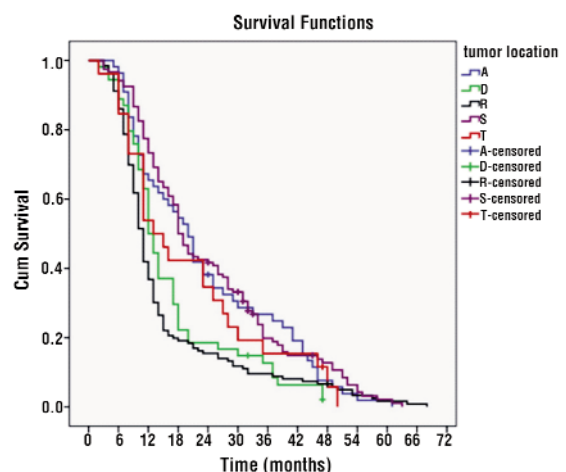


Figure 4. Survival curves Kaplan Meier depending on tumor location

The risk of death in patients with carcinomatosis was $-HR = 2.631$, 95% CI (1.897, 3.648) (p value = 0.000000). The 5-years survival of patients with peritoneal carcinomatosis is 0%, while in patients without peritoneal carcinomatosis, the 5-years survival is 1.7% (*Table 1*).

Of the 68 patients with liver metastases, none survived until 01.10.2019. Of the 323 patients without liver metastases, 12 (3.7%) survived by the end of the study. Comparing the survival on the 2 groups, there is a statistically significant difference (p _value = 0.000000 Log Rank (Mantel-Cox)).

The risk of death in patients with hepatic metastases was $-HR = 2.271$, 95% CI (1.959, 2.633) (p value = 0.000000). The 5-years survival of patients with hepatic metastases is 0%, while in patients without hepatic metastases, the 5-years survival is 2.0% (*Table 1*).

Of the 155 patients with colostomies, 154 died and 1 (0.6%) survived until 01.10.2019. Of the 124 patients who underwent Hartmann interventions, 117 died and 7 (5.6%) were alive at the end of the study. Of the 27 patients who underwent internal derivations, none survived until the end of the study and of the 85 patients with resections with anastomosis, 81 died and 4 (4.7%) survived until the end of this study. Comparing the survival on the 4 groups, we found a statistically significant difference (p _value = 0.000000 Log Rank (Mantel-Cox)), more precisely: significant differences between patients with colostomies and those with Hartmann operations (p value = 0.000000), between those with colostomies and those with resections with anastomosis (p value = 0.000057), between those with Hartmann operations and those with internal derivations (p value = 0.000000), but also between those with internal derivations and those with resections with anastomosis (p value = 0.000000) (*Fig. 5*).

The risk of death in patients with colostoma was $-HR = 2.405$, 95% CI (1.827, 3.166) (p _value = 0.000000), and of those with internal derivatives $-HR = 7.693$, 95% CI (4.797, 12.338) (p _value = 0.000000), compared with those with resection-anastomosis.

The 5-years survival of patients with colostomies is 1.5%, of those with Hartmann's operations is 2.2%, of those with internal derivations is 0% and for those with resections with anastomosis 1.5% (*Table 1*).

Of the 76 patients who underwent lymph node dissection during the emergency intervention, 72 died and 4 (5.3%) survived until 01.10.2019. Of the 315 patients without lymph node dissection, 307 died and 8 (2.5%) were alive at the end of the study. Comparing the survival on the 2 groups, there is a statistically significant difference (p _value = 0.000001).

The risk of death in patients with lymph node dissection was $-HR = 0.737$, 95% CI (0.648, 0.839) (p value = 0.000004). The 5-years survival of patients with lymph node dissection is 1.6%, while in patients without lymph node dissection, the 5-years survival is 1.2% (*Table 1*).

Of the 14 patients who underwent hepatic biopsy of tumor formations with metastasis appearance, 13 died and 1 (7.1%) survived until 01.10.2019. Of the 377 patients without liver biopsy, 366 died and 11 (2.9%) were alive at the end of the study. Comparing the survival on the 2 groups, there is a statistically significant difference (p _value = 0.043483).

The risk of death in patients with liver biopsy was $-HR = 1.316$, 95% CI (0.996, 0.839)

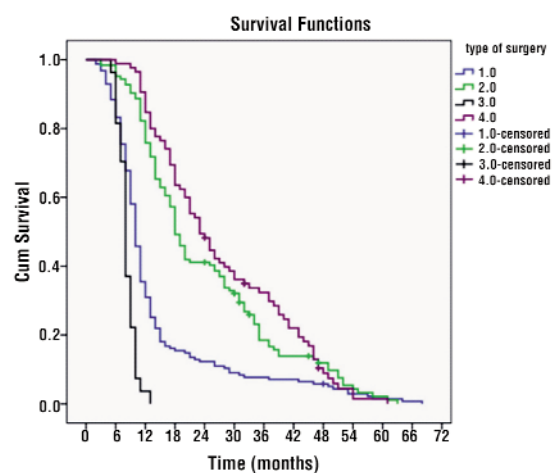


Figure 5. Survival curves Kaplan Meier according to the type of surgery

(p value = 0.000004). The 5-years survival of patients with liver biopsy was 0%, while in patients without liver biopsy, the 5-years survival was 1.7% (Table 1).

Of the 57 patients who underwent stoma reversal after Hartmann interventions, 49 died and 8 (14%) survived until 01.10.2019. Of the 201 patients without stoma reversal, none survived until the end of the study. Comparing the survival on the 2 groups, there is a statistically significant difference (p_value = 0.000000).

The risk of death for patients with reintegration was $\text{HR} = 0.175$, 95% CI (0.124, 0.247) (p value = 0.000000). The 5-years survival of patients with reintegration is 4.9%, while in patients without reintegration, the 5-years survival is 0% (Table 1).

Of the 80 patients who underwent serial interventions, 72 died and 8 (10%) survived until 01.10.2019. Of the 228 patients without serial interventions, none survived until the end of the study. Comparing the survival on the 2 groups, there is a statistically significant difference (p_value = 0.000000).

The risk of death for patients with serious interventions was $\text{HR} = 0.216$, 95% CI (0.167, 0.279) (p value = 0.000000). The 5-years survival of patients with serial interventions is 6.4%, while in the patients without serial interventions, the 5-years survival is 0% (Table 1).

Of the 106 patients with stage II pTNM, 96 died and 10 (9.4%) survived until 01.10.2019. Of the 216 patients with stage III pTNM, 214 died and 2 (0.9%) were alive at the end of the study. Of the 69 patients with stage IV pTNM, none survived until the end of the study. Comparing the survival in the 3 groups, we found a statistically significant difference (p_value = 0.000000), more precisely, significant differences were obtained between the stages pTNM II-III, II-IV and III-IV (p_value = 0.000000) (Fig. 6).

The mortality risk in stage 3 patients was $\text{HR} = 25,482$, 95% CI (15,585, 41,663) (p_value = 0.000000), and of those with stage 4 $\text{HR} = 105,648$, 95% CI (59,575, 187,354) (p_value = 0.000000), compared to those with stage 2.

The 5-years survival for cases in stage II pTNM is 5.9%, while in the patients with stages III and IV pTNM, the 5-years survival is 0% (Table 1).

Of the 106 patients with well-differentiated tumors, 101 died and 5 (4.7%) survived until 01.10.2019. Of the 251 patients with moderate-differentiated tumors, 244 died and 7 (2.8%) were alive at the end of the study. Of the 34 patients with poorly differentiated tumors, none survived until the end of the study. Comparing the survival on the 3 groups, we found a statistically significant difference (p_value = 0.007069), more precisely: a significant difference between grading 1 and 3 (p_value = 0.002739) and between grading 2 and 3 (p_value = 0.004252) (Fig. 7).

The risk of death in patients with poorly differentiated tumors was $\text{HR} = 1,814$, 95% CI (1,224, 2,689) (p_value = 0.003003) compared to well differentiated tumors. The 5-years survival for grade 1 tumors is 1.4%, in patients with grade 2 tumors, the 5-year survival is 1.9% and for those with grade 3 tumors is 0% (Table 1).

Multivariate Analysis

We entered the data after eliminating the variables without statistical significance, and selected the final values with statistical significance.

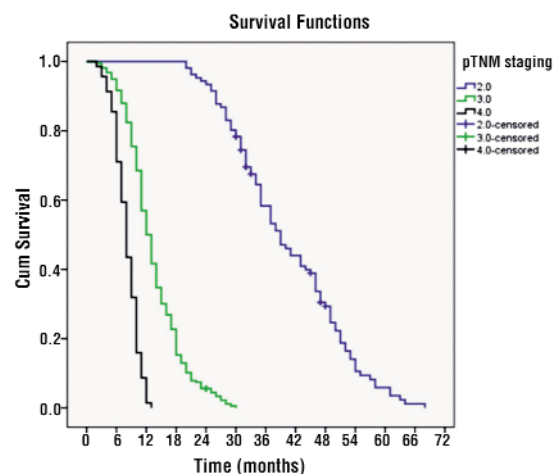


Figure 6. Survival curves Kaplan Meier according to pTNM staging

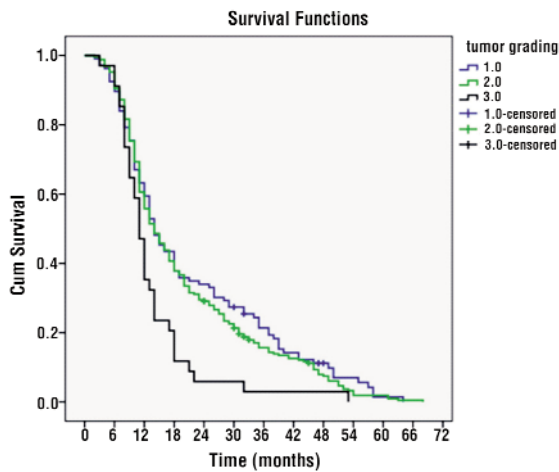


Figure 7. Survival curves Kaplan Meier according to tumor grading

Comparing the survival in patients aged > 61 with those < 61 , but with the same values for cachexia, carcinomatosis, type of operation, stage of disease and serial interventions, the risk of death in patients > 61 years old were calculated -HR = 1.026, 95% CI = (1.012, 1.039) ($p_{\text{value}} = 0.000139$) (Table 1), so age > 61 is an independent risk factor.

Comparing the survival in patients with cachexia with those without cachexia, but with the same values for age, carcinomatosis, type of operation, stage of disease and serial interventions, the risk of dying was calculated for patients with cachexia - HR = 1,358, 95% CI = (1,046, 1.764) ($p_{\text{value}} = 0.021617$) (Table 1), so the presence of cachexia was demonstrated as an independent risk factor. Survival comparison of cases with peritoneal carcinomatosis with those without carcinomatosis, but with the same values for the other variables, the risk of death was calculated for patients with carcinomatosis - HR = 2,346, 95% CI = (1,163,4,732) ($p_{\text{value}} = 0.017253$) (Table 1), so the presence of peritoneal carcinomatosis is an independent risk factor.

Comparing the survival in patients with Hartmann operations with those with internal derivations, but with the same values for age, cachexia, carcinomatosis, disease status and serial interventions, the risk of dying was calculated for patients with Hartmann

procedure - HR = 0.187, 95 % CI (0.045, 0.779) ($p_{\text{value}} = 0.021281$) (Table 1), so the Hartmann procedure is an independent protection factor.

Analyzing patients with stage IV compared with those with stage II, but with the same values for the other variables, the risk of dying was calculated for patients with stage IV tumors - HR = 36,745, 95% CI = (14,778, 91,366) ($p_{\text{value}} = 0.000000$) (Table 1), so stage IV is an independent risk factor.

Analyzing life span in patients diagnosed with stage III with those on stage II, but with the same values for the other variables, the risk of death was calculated in the case of patients with tumors in stage III - HR = 11,114, 95% CI = (4,835, 25.59566) ($p_{\text{value}} = 0.000000$) (Table 1), so stage III disease is an independent risk factor.

Comparing the survival in patients with serial interventions with those without such interventions, but with the same values for age, cachexia, carcinomatosis, with Hartmann procedure, stage III or IV, the risk of death was calculated in patients with serial interventions - HR = 0.282, 95% CI = (0.144,0.551) ($p_{\text{value}} = 0.000213$) (Table 1), so serial interventions are an independent protection factor.

Discussions

In our study, we showed that survival of the patients with colorectal cancer in the long-term is negatively influenced by: the age of the patients (> 61 years), the presence of abdominal surgical history, the presence of associated cardiac diseases, especially the atrial fibrillation, the preoperative diagnosis (diastatic perforation imminence), the presence of cachexia, oliguria, anemia and the hydro-electrolyte disorders at admission, the location of the tumors at the rectal level, the presence of the tumor invasion in other organs, the appearance of "frozen pelvis", the hepatic metastases and the peritoneal carcinomatosis, the type of surgery (internal derivations), absence of lymph node dissection, absence of stoma reversal or practicing serial interventions, stage IV p TNM and poorly differentiated tumors.

The multivariate analysis that we performed revealed the independent prognostic factors: age over 61, the presence of cachexia, peritoneal carcinomatosis, stage III and IV, while Hartmann procedure and serial interventions were independent protection factors.

In most studies, the advanced age of patients with colorectal cancer, operated in emergency, was a risk factor (13-15), as in our study. Other studies have reported a poor prognosis in young patients with colorectal neoplasm. Young patients are considered to have a poorer prognosis due to the association with the presence of undifferentiated tumors (16-19). On the contrary, in other studies it is shown that younger patients have a better survival, explained in the first place by the fact that they present in a better biological state and thus allow us to practice larger interventions (20).

The data from various published works indicate a statistically significant correlation between the long-term survival of complicated colorectal cancer cases and the association of comorbidities (21, 22), a correlation that we also found in our study.

Regarding the preoperative diagnosis, in our study we showed that the imminence of diastatic perforation was a risk factor. Studies on this subject are lacking. Most attribute better long-term survival to hemorrhagic tumors, possibly due to the patients' alarming and thus to an earlier presentation and diagnosis (23).

Neoplastic cachexia is a complex condition, which involves systemic inflammation, negative protein and energy balance and involuntary loss of body mass, with or without fat loss (24). In our study, neoplastic cachexia was an independent prognostic factor. Literature publications on this topic are missing.

A recent study published in Brazil, shows that anemia is a risk factor for colorectal cancer patients operated in emergency (25), as it happened in our study, and anemia with preoperative transfusion was an independent risk factor, correlation that we did not find.

There are divergent opinions about how the tumors' location on different segments could

influence the survival. One study showed that the location of the tumor under the reflection of the peritoneum on the rectum (subperitoneal rectum) decreases the 5-years survival compared to the locations on the

intraperitoneal rectum and those on the colon (26). We also found this fact in our study. Some authors have shown that primary tumors located on the left colon were associated with significantly lower risk of death and concluded that tumor location should be a criterion for establishing the prognosis (27, 28).

The tumor invasion in other organs was a negative prognostic factor in our study, similar to other published research (29-32).

The metastases of colorectal tumors occur most frequently in the liver, given the location of this organ in relation to the portal circulation (33). The presence of liver metastases is a unanimous negative prognostic factor for colorectal cancer patients (34,35), even more for those operated in emergency.

In some studies, the colorectal cancer with peritoneal carcinomatosis operated in emergency, has been associated with the lowest survival (7). A whole series of studies that analyzed the tumor invasion of the peritoneal serous as a separate variable, have shown in multivariate analyzes, that this is an independent negative prognostic factor (36), as we have found in our study.

The results of most published studies agree that emergency surgery itself is a negative prognostic factor for the long-term survival of colorectal cancer patients (37-39).

In a study conducted recently at the University Hospital in Daejeon, Korea, it is shown the importance of choosing the type of surgery for colorectal cancer patients. The highest mortality was recorded in patients with colostomy, similar to the data from our study (40).

Regarding the lymph node dissection, its practice has proved to be a risk factor in our study, similar to the reports of other authors (41), but different than others' results (42,43).

In a recent study conducted at Basel University Hospital, Switzerland, which included 747 colorectal cancer patients, 84 of

which being operated in emergency, between 1989-2013, the authors showed that age, tumor location, lymphadenectomy and tumor status were independent prognostic factors for long-term survival (44).

Similar to our data, the practice of serial interventions has been shown to be a protective factor in other studies (15, 45-47). In contrast, other authors concluded that resections with anastomosis ensure better survival, including for occlusive tumors (48).

The stoma reversal after Hartmann procedures was also a protection factor in other studies (49,50). For the patients in our group, stoma reversal was performed at an average interval of 5.7 months. In the literature, it is recommended that the restoration of the transit should be done at 6-10 months, but not later. The experience from the Dutch Rectal Cancer trial has shown that if a colostomy is not closed in the first year after surgery, it will most likely become permanent (51).

In a prospective study conducted at Cornwall Hospital in the United Kingdom, the authors demonstrated that the most important prognostic factor for long-term survival was the tumor stage (15).

Very recent studies reaffirm the significant correlation between the advanced stage of the disease (III and IV) and the long-term survival in cases with complicated colorectal cancer (52). Other authors found statistical significance only in the association of stage IV with the long-term survival (53). Some authors considered that for the stage IV of the disease, the percentage of survivors is so low that they excluded these patients from the survival analysis (54).

In our study, we also found statistical significance in correlating tumor grading with the long-term survival of patients with complicated colorectal cancer, as confirmed by other authors (55).

Conclusions

1. For cases with colorectal tumors operated in emergency, the risk factors associated with overall survival were: the age > 61, the presence of abdominal surgical history

and associated cardiac conditions, especially atrial fibrillation, diagnosis of diastolic perforation imminence, cachexia, oligoanuria, anemia and hydro-electrolyte disorders at admission, rectal tumors, tumor invasion in other organs, appearance of "frozen pelvis", presence of hepatic metastases or peritoneal carcinomatosis, stage IV tumors, practicing of internal derivations or not performing lymph node dissection.

2. In the multivariate regression analysis we found that age over 61, cachexia, peritoneal carcinomatosis, as well as stage III or IV of the disease are independent risk factors and Hartmann procedure and serial interventions are independent protective factors.

Conflict of Interest

The authors declare no conflicts of interests.

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