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Research Article

Thirty-day postoperative mortality in colon cancer surgery. A single-center analysis of 630 patients

[1,2]Miana Gabriela Pop, [1,2]Dana Monica Bartoș, [3]Ana Maria Fiț, [4]Ștefan Cristian Vesa, [2]Adrian Bartoș, [2]Iancu Cornel

[1] Department of Anatomy and Embriology, "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania; [2] Department of General Surgery, "Octavian Fodor" Regional Institute of Gastroenterology and Hepatology, Cluj-Napoca, Romania; [3] Department of Anatomic Pathology, "Octavian Fodor" Regional Institute of Gastroenterology and Hepatology, Cluj-Napoca, Romania; [4] Department of Pharmacology, Toxicology and Clinical Pharmacology, "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania.

Abstract. Objective: Colon cancer surgery may result in postoperative complications, influencing 30-day postoperative mortality. Postoperative mortality may be an indicator of the quality of treatment, can be consecutive to important comorbidities or can be related to other perioperative factors. Adjusting factors that influence 30-day mortality may improve long-term outcome of patients undergoing surgery for colon cancer. The aim of this study was to identify risk factors for 30-day postoperative mortality in a cohort of patients operated in a single tertiary center. Material and Method: Patients diagnosed with colon cancer between January 2013 and December 2015 that underwent surgery in one tertiary center were included in the study. Patient demographics, comorbidities, preoperative biological parameters, tumor and surgery-related factors alongside with postoperative complications were analyzed in relation to 30-day postoperative mortality. Results: The rate of 30-day postoperative mortality was observed in 25 patients (3.9%). Univariate analysis revealed that factors such as age over 63 years (p=0.02), type II diabetes (p=0.01), type of surgery (elective or emergency) (p=0.01), presence of ileus (p=0.02), postoperative respiratory (p=0.01) and cardiovascular complications (p=0.01), postoperative hemorrhagic complications (p=0.009), anastomotic fistula (p=0.01), intra-abdominal abscesses (p=0.04), postoperative evisceration (p=0.04), acute renal failure (p=0.009), urea >48 U/l (p=0.01), creatinine >1.19 mg/dl (p=0.01), and preoperative mechanical bowel preparation of the colon (p = 0.01) significantly influence postoperative mortality. Following multivariate analysis, emergency surgery (OR 4.233, CI95% 1.235 – 9.899, p=0.01), postoperative respiratory complications (OR 5.445, CI95% 1.240-23.901, p=0.025) and postoperative hemorrhage (OR 24.185, CI95% 1.867-313.365, p=0.015) are independent variables associated with the 30-day mortality in colon cancer surgery. Conclusion: Emergency surgery along with postoperative respiratory and hemorrhagic complications are risk factors for 30-day mortality after colon cancer surgery.

Key Words: colon cancer, surgery, mortality, risk factors, complications.

Corresponding Author: D. M. Bartoș, email: bartosdanamonica@gmail.com

Introduction

Colon cancer is the third most common cancer worldwide, being ranked third to breast and lung cancer in women, respectively third to prostate and lung cancer in men (Siegel et al 2018). The treatment of choice in the majority of colorectal cancers is radical surgery with curative intent, with or without chemotherapy as adjuvant therapy. Colon cancer surgery may result in postoperative complications, influencing 30-day mortality. Postoperative mortality is an indicator of the quality of surgery but also of the level of postoperative care, being used in some countries as a criterion for differential funding of health institutions. In what concerns surgery for colorectal cancer, literature data rates 30-day postoperative mortality between 1.9 and 6.9% (Sutherland et al 2014, Rasouli et al 2017, Bakker et al 2014, Van Eeghen et al 2015, Mik et al 2014, Gooiker et al 2012, Mooris et al 2011). Factors reported in the literature as having a negative impact on 30-day postoperative mortality are advanced age at diagnosis (Rasouli et al 2017, Sutherland et al 2014, Mooris et al 2011, de Vries et al 2014), associated comorbidities (Rasouli et al 2017, Sutherland et al 2014, Mooris et al 2011), advanced tumor stage (de Vries et al 2014), poorly differentiated tumors (Rasouli et al 2017, Mooris et al 2011, Mik et al 2014), emergency surgery (Rasouli et al 2017, Sutherland et al 2014, Mooris et al 2011, Mik et al 2014, de Vries et al 2014), postoperative complications like anastomotic leak (Tevis et al 2016, Krarup et al 2012), intra-abdominal infection (Tevis et al 2016, Krarup et al 2012), prolonged ileus (Tevis et al 2016), hemorrhage (Tevis et al 2016, Tasu et al 2015) and cardiorespiratory complications (Tevis et al 2016) but also patients of low socioeconomic status (Rasouli et al 2017, Mik et al 2014).

Identifying and correcting factors that influence postoperative mortality allows for surgical quality improvement and increased survival rates in patients with colorectal cancer. The purpose of this study was to analyze 30-day postoperative mortality rate as well as the risk factors that influence it in patients with colorectal cancer operated in a single tertiary care center.

Materials and methods

Study design

This is a longitudinal, observational, analytical, cohort study of 630 patients diagnosed with colorectal cancer between January 2013 and December 2015, undergoing surgery in a single tertiary center. Patients with rectal neoplasia or those who had undergone colectomy for benign colorectal neoplasia were excluded from the study. All patients signed the inform consent for inclusion in the study.

Data collection

Data were collected from the center's database and the medical records of the patients in a prospective way. Patient demographics were recorded (gender, age at diagnosis), associated comorbidities (ischemic heart disease, cirrhosis, kidney disease, type I and type II diabetes mellitus, history of surgery, associated neoplasms, ASA score), tumor-related data (tumor localization, TNM tumor stage, degree of cancer cell differentiation, type of neoplasia - adenocarcinoma, mucinous carcinoma, signet cell neoplasia, lymphatic invasion, venous invasion, resection margins), surgery-related data (type of hospitalization - elective or emergent, patients who presented with occlusive disease or intestinal perforation due to colon cancer, type of surgery - conventional or laparoscopic, multiorgan resection, protective ileostomy, intraoperative blood loss and preoperative mechanical bowel preparation) as well as biological data (hemoglobin, urea and creatinine levels, proteinemia). Postoperative complications analyzed in relation to 30-day mortality were anastomotic fistula, intra-abdominal abscess, postoperative hemorrhage, postoperative ileus, evisceration, surgical wound infection, postoperative respiratory and cardiac complications, pulmonary thromboembolism and acute renal failure.

Statistical analysis

Statistical analysis was performed using MedCalc Statistical Software version 17.9.7 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2017). Categorical variables were reported using frequency and percentage, while continuous ones were expressed as median and interquartile range. For categorical variables the Chi-square test was used to determine the differences between groups, and the Mann-Whitney test was applied for quantitative data. The area under the ROC (AUROC) was used to assessed the relationship of some continuous variables with mortality. Cut-off values were chosen were sensibility and specificity were maximum. Variables that achieved significance in univariate analysis were further introduced in multivariate logistic regression. A $p < 0.05$ value was considered statistically significant.

Table 1. Demographic and clinical characteristics of the patients with colon cancer

Variables		n (%)
Gender	F	268 (42.5)
	M	362 (57.5)
Alcohol		104 (16.5)
Type I diabetes		2 (0.3)
Type II diabetes		91 (14.4)
Ischemic heart disease		165 (26.2)
Kidney disease		22 (3.5)
Colorectal polyps		27 (4.3)
Colonic diverticulitis		28 (4.4)
Cirrhosis		7 (1.1)
Associated neoplasms		28 (4.4)
History of surgical interventions		90 (14.3)
Type of surgery	Elective	512 (81.3)
	Emergency	118(18.7)
Tumor localization	Ascending colon	235 (37.3)
	Transverse colon	13 (2.06)
	Descending colon	72 (11.4)
	Sigmoid colon	310 (49.2)
Stage	I	79 (12.5)
	IIA	183 (29)
	IIB	31 (4.9)
	IIC	24 (3.8)
	IIIA	24 (3.8)
	IIIB	154 (24.4)
	IIIC	90 (14.3)
	IVA	19 (3)
	IVB	26 (4.1)
Hystopatologic result	Adenocarcinoma	551 (87.4)
	Mucinos adenocarcinoma	63 (10)
	Signet cell carcinoma	16 (2.6)
Grading	G1	120 (22.2)
	G2	329 (60.8)
	G3	92 (17)
	Unknown	89 (14.12)

Results

Demographic and clinical characteristics of the 630 patients included in the study are shown in Table 1.

In this study group, 30-day mortality was observed in 25 patients (3.9%). Patient and surgery-related factors but also postoperative complications that influenced 30-day mortality in univariate analysis are presented in Table 2.

We calculated for age a cut-off value of 63 years, over which the chances of death increased (AUC 0.681, Se 92%, Sp 40.8%; $p<0.001$); for urea a cut-off value of 48 U/l (AUC 0.835, Se 80%, Sp 76.4%; $p<0.001$); for creatinine a cut-off value of 1.19 mg/dl (AUC 0.811, Se 68%, Sp 85.6%; $p<0.001$). Gender ($p=0.19$), smoking ($p=0.10$), alcohol consumption ($p=0.94$) or comorbidities like ischemic heart disease ($p=0.16$), kidney disease ($p=0.06$), cirrhosis ($p=0.58$), colorectal polyps ($p=0.93$) or diverticulitis ($p=0.62$), type I diabetes ($p=0.77$), history of surgical intervention ($p=0.13$), associated neoplasm ($p=0.91$), hemoglobin level ($p=0.06$), total protein level ($p=0.80$), ASA

Table 2. Univariate analysis of significant factors in relation to 30-day postoperative mortality

Variables		Survivors (n,%)	Deceased (n,%)	p
Patient-related factors				
Age >63		66 (58.75 ; 73)	75 (64;81)	0.02
Urea >48 U/l		44 (30.75 ; 56)	86 (72; 94)	0.01
Creatinine >1.19 mg/dl		0.94 (0.75 ; 1.16)	2.01 (1.23; 5.38)	0.01
Type II diabetes		83 (91.2)	8 (8.8)	0.01
Surgery-related factors				
Hospitalization type	**Elective**	497 (97.07)	15 (2.93)	0.01
	Emergency	108 (91.52)	10 (8.48)	
Reason for presentation – occlusive colon tumor		71 (91.02)	7 (8.98)	0.02
Preoperative mechanical bowel preparation		351 (97.77)	8 (2.23)	0.01
Postoperative complications				
Anastomotic fistula		20 (83.33)	4 (16.67)	0.01
Intra-abdominal abscess		0 (0)	1 (100)	0.04
Postoperative hemorrhage		2 (50)	2 (50)	0.009
Eviscerations		7 (77.78)	2 (22.22)	0.04
Respiratory complications		9 (60)	6 (40)	0.01
Cardiovascular complications		0 (0)	7 (100)	0.01
Pulmonary thromboembolism		1 (50)	1 (50)	0.07
Acute renal failure		2 (50)	2 (50)	0.009

Table 3. Evaluation of independent risk factors for 30-day mortality in multivariate analysis

Variables	p	OR	95% CI
Age >63	0.054	5.32	0.97 – 29.14
Urea >48 U/l	0.07	3.24	0.90 – 11.57
Creatinine >1.19 mg/dl	0.21	2.07	0.66 – 6.49
Type II diabetes	0.205	2.1	0.66 – 6.67
Emergency surgery	0.01	4.23	1.23 – 9.89
Preoperative mechanical bowel preparation	0.202	0.49	0.16 – 1.45
Postoperative complications – anastomotic fistula	0.267	2.82	0.45 – 17.58
Postoperative complications – intra-abdominal abscess	0.201	0.58	0.24 – 1.55
Postoperative complications - hemorrhage	0.015	24.18	1.86-313.36
Postoperative complications – eviscerations	0.414	2.42	0.28 – 20.29
Postoperative complications – respiratory complications	0.025	5.44	1.24-23.90
Postoperative complications – cardiovascular	0.061	3.11	0.880 – 7.89
Postoperative complications – acute renal failure	0.094	4.55	0.70 – 11.56

score (p=0.21), blood loss (p=0.56) and resumption of intestinal transit (p=0.51) were patient-related factors analyzed in relation to 30-day postoperative mortality that did not achieved statistical significance. Regarding tumor-related factors, none of the variables analyzed achieved statistical significance in univariate analysis. Type of surgery (elective or emergency) p=0.01, presentation with occlusive colon cancer (p=0.02) and preoperative mechanical bowel preparation of the colon (p=0.01) are the variables that influence postoperative mortality in colon cancer surgery (Table 2) while surgical approach (laparoscopic vs conventional) p=0.18, anastomotic suture (mechanical vs hand-sewn) p=0.12, presentation with intestinal perforation (p=0.57) and protective ileostomy (p=0.61) are surgery-related factors that did not achieved statistical significance in relation to 30-day postoperative mortality.

From all colon cancer patients included in the study, 93 (14.7%) presented with postoperative complications. The most frequent postoperative complication was anastomotic fistula, which occurred in 24 (3.8%) patients, followed by surgical wound infection in 22 (3.4%) patients. The variables that obtained statistical significance in univariate analysis are presented in Table

2. Postoperative ileus (p=0.18) and wound infection (p=0.21) are not significant factors for 30-day postoperative mortality.
Following multivariate analysis, emergency surgery (OR 4.23), postoperative respiratory complications (OR 5.44) and postoperative hemorrhage (OR 24.18) are risk factors for 30-day mortality. The rest of the variables processed in the multivariate analysis did not achieve statistical significance (Table 3).

Discussions

Of all the comorbidities analyzed in the present study in relation to 30-day mortality, type II diabetes was the only parameter that obtained statistical significance in univariate analysis. However, the condition did not achieve statistical significance following multivariate analysis. The result differs from that of other studies where an increase in 30-day mortality rate was observed in patients with type II diabetes (Mik et al 2014, Chen et al, 2014, Fransgaard et al 2016, Van Eeghen et al 2015). In this paper, we did not have the possibility to distinguish between compensated and uncompensated diabetes mellitus (best reflected through the level of the glycated hemoglobin-HbA1c), which could be more useful in assessing postoperative mortality and that could be the point of future research in our department.
Similarly, the advanced age of patients (over 63 years) did not increase 30-day postoperative mortality rate in the present study, although initially the variable had statistical significance in univariate analysis. According to other studies, (Morris et al 2011, Idehioda et al 2013) elderly patients undergoing surgery for colon cancer are at risk for 30-day postoperative mortality. However, the reference point for these studies was higher (over 80 years), condition that could explain the result. In our study population group, age over 63 is not a contraindication for surgery but further studies are necessary to evaluate the subgroup of patients age 80 and over.
Emergency surgery has a negative impact on 30-day postoperative mortality in this study, result which is consistent with other papers (Sutherland et al 2014, Bakker et al 2014, Morris et al 2011, Mik et al 2014). Emergency surgery is mainly performed for complications of the colon cancer, like intestinal perforation, hemorrhage or occlusive tumor. Operations performed in emergency are characterized by increase difficulty and are more subjected to complications compared to elective procedures due to several aspects: the lack of appropriate patient investigation, lack of adequate patient preparation and biological stabilizationand, not least, most of the surgeries are performed during night-shifts in tired conditions for the surgical team. Emergency presentation with complicated colorectal cancer may require surgery in delicate conditions, with increase difficulty, which could explain the result in our study. Patients who need emergent colon resections are considered to be at high risk for postoperative mortality and need, thus, close monitoring.
Among the variables analyzed in this study, postoperative complications had the most important impact on 30-day mortality. However, after multivariate analysis, only postoperative respiratory complications (OR 5.445) and postoperative hemorrhage (OR 24.185) maintained statistical significance.
Thus, postoperative respiratory complications are independent predictors of increased mortality in patients undergoing surgery for colorectal cancer. The results are similar to those obtained in other studies (Platon et al 2014, Matsuyama et al, 2013, Kim et al 2016). Mostly, postoperative respiratory complications are related to prolonged surgery requiring long anesthesia (Davies et al 2017), to large intraoperative blood loss with transfusion requirements, condition that can lead to TRALI – transfusion related acute lung injury (Clifford et al 2015) and to postoperative analgesia (abdominal pain prevents expansion of the thoracic cavity and inadequate pulmonary ventilation) but some studies also incriminated the use of the naso-gastric tube before surgery (for gastric and bowel decompression in occlusive colon cancer disease, but most to avoid pulmonary aspiration) (Davies et al 2017). Not least, according to some studies, postoperative respiratory complications occur more frequently after emergency surgeries, having a higher rate for postoperative mortality compared with the ones that appear after elective procedure (Kim et al 2016, Canet et al 2015).
Patients undergoing colon cancer surgery have a risk between 5-9% to develop postoperative hemorrhage (Tevis et al 2016, Tasu et al 2015). In the present study, the postoperative hemorrhagic episode appeared in 4 (4.3%) of the cases and was also found to be a risk factor for 30-day mortality. Reducing the number and severity of postoperative hemorrhagic complications can be achieved by an accurate hemostasis performed intraoperatively but also by a correct management of an preexisting coagulopathy.
To conclude, early-stage colon cancer diagnostic is essential to avoid late-stage presentation with complications of the disease that require urgent interventions. Pulmonary complication in colon cancer surgery are a cause of 30-days postoperative mortality and should be carefully monitored in patients at risk. The occurrence of postoperative hemorrhage should be avoided by adequate intraoperative hemostasis and by careful monitoring and correction of coagulation disorders.
Study limitations: Postoperative complications were recorded without considering their severity. Data relating surgeons experience were also missing.

Conclusions

Emergency surgery along with postoperative respiratory and hemorrhagic complications are risk factors for 30-day mortality after colon cancer surgery.

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Authors

•Miana Gabriela Pop, Anatomy and Embriology Department, "Iuliu Haţieganu" University of Medicine and Pharmacy, 3-5th Clinicilor Street, 400139, Cluj-Napoca, Romania, EU; "Octavian Fodor" Regional Institute of Gastroenterology and Hepatology, 19-21 Croitorilor Street, 400162, Cluj-Napoca, Romania, email: mianagabrielapop@gmail.com

•Dana Monica Bartoş, Anatomy and Embriology Department, "Iuliu Haţieganu" University of Medicine and Pharmacy, 3-5th Clinicilor Street, 400139, Cluj-Napoca, Romania, EU; "Octavian Fodor" Regional Institute of Gastroenterology and Hepatology, 19-21 Croitorilor Street, 400162, Cluj-Napoca, Romania, email: bartosdanamonica@gmail.com

•Ana Maria Fiț, Department of Anatomic Pathology, "Octavian Fodor" Regional Institute of Gastroenterology and Hepatology, 19-21 Croitorilor Street, 400162, Cluj-Napoca, Romania, email: fitanamaria@yahoo.com

•Ștefan Cristian Vesa, Department of Pharmacology, Toxicology and Clinical Pharmacology, "Iuliu Haţieganu" University of Medicine and Pharmacy, 23 Gheorghe Marinescu Street, 400337, Cluj-Napoca, Romania, EU, email: stefanvesa@gmail.com

•Adrian Bartoş, "Octavian Fodor" Regional Institute of Gastroenterology and Hepatology, 19-21 Croitorilor Street, 400162, Cluj-Napoca, Romania, email: bartos.adi@gmail.com

•Iancu Cornel, "Octavian Fodor" Regional Institute of Gastroenterology and Hepatology, 19-21 Croitorilor Street, 400162, Cluj-Napoca, Romania, email: dr.iancu.cornel@gmail.com

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