

Predictors of 1-year postoperative mortality in radical colon cancer surgery



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AIM: *The aim of this study was to determine the impact of patient, tumor and surgery-related parameters on 1-year postoperative mortality in a cohort of patients operated in a single tertiary center.*

MATERIALS AND METHODS: *The study included 605 patients diagnosed with colon cancer between January 2013 and December 2015 that underwent radical surgery in a tertiary center. Patient demographics, comorbidities, preoperative biological parameters alongside with tumor and surgery-related factors were prospectively recorded and then analyzed in relation 1-year postoperative mortality.*

RESULTS: *One-year mortality rate in the study group was 10.9%. Independent risk factors in relation to 1-year mortality were advanced TNM stage (OR 3.10, 1.10 – 8.75 95% CI), emergency surgery (OR 1.91, 1.11 – 3.74 95% CI), location of the tumor in the ascending colon (OR 2.17, 1.32 – 3.57 95% CI), multiorgan resections (OR 2.07, 1.15 – 3.74 95% CI), age over 63 years (OR 2.05, 1.16 – 3.62 95% CI) and the history of alcohol consumption (OR 2.058, 1.17 – 3.61 95% CI).*

DISCUSSION: *Postoperative complications are still being reported in colon cancer surgery, despite technological progress and constant research in the field. So far, factors that influence postoperative mortality have been mostly studied up to 30 days postoperatively. According to some recent papers, reporting 30-day mortality data can underestimate accurate communication of postoperative adverse events. Thus, 1-year mortality in colon cancer surgery could be a better indicator of the impact on surgery on postoperative period of this patients and factors that influence it should be well known.*

KEY WORDS: Surveillance, Colon cancer, 1-year mortality

Introduction

Colon cancer continues to be a common neoplastic disease which in women is ranked second after breast cancer and in men third after prostate and lung cancer ¹.

Standard treatment in colon cancer remains the surgical resection of the tumor accompanied or not by chemotherapy as adjuvant therapy. Postoperative mortality and factors that influence its occurrence still represent a widespread subject and a matter of intense research in literature.

The majority of literature research papers evaluate and report postoperative mortality as the number of deaths that occur within a range of 30 days after surgery ²⁻⁶. However, recent studies started to recommend the use of 1-year mortality rate as a better tool for evaluation of the postoperative mortality in colon cancer surgery ⁷⁻¹⁰. Arguments in favor of this hypothesis are several studies that confirm the existence of a high mortality rate

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beyond 30-days and who consider that 30-day mortality underestimates postoperative mortality after colonic resections^{7,9,11}. More, this papers also highlighted the need for an accurate identification of neoplastic patients at risk for postoperative adverse events and also the factors that could influence 1-year postoperative mortality. The aim of our study was to determine 1-year mortality rate and to evaluate the impact of patient, tumor and surgery-related parameters on 1-year postoperative mortality in a cohort of patients that underwent surgery for colon cancer in a single tertiary center.

Material and Method

STUDY DESIGN

This is a prospective, longitudinal, observational, analytical, cohort study of 605 patients diagnosed with colon cancer between January 2013 and December 2015, undergoing surgery in one tertiary center. Patients under the age of 18, pregnant women, patients with tumors under 15cm from the anal verge or those with benign colonic tumors were excluded from the study. All patients signed the inform consent for inclusion in the study. The study protocol was approved by the Ethics Committee of the institute.

DATA COLLECTION

Data were collected from the institution's database in a prospective manner. The following variables have been recorded: patient demographics (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 14-18g/dl, urea 18-48 mg/dl and creatinine 0.67 - 1.17 mg/dl levels, proteinemia 6-8 g/dl). 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 assess 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 I - Demographic and clinical characteristics of the patients.

Variables	n (%)
Gender	
F	261 (43.1)
M	344 (56.9)
Smoking	26 (4.3)
Alcohol	100 (16.5)
Type I diabetes	2 (0.3)
Type II diabetes	83 (13.7)
Ischemic heart disease	155 (25.6)
Kidney disease	19 (3.1)
Colonic polyps	24 (4.3)
Colonic diverticulitis	28 (4.6)
Cirrhosis	7 (1.2)
Associated neoplasms	27 (4.5)
History of surgical interventions	89 (14.7)
Type of surgery	
Elective	497 (82.1)
Emergency	108 (17.9)
Tumor localization	
Ascending colon	227 (37.5)
Transverse colon	13 (2.1)
Descending colon	68 (11.2)
Sigmoid colon	299 (49.4)
Stage	
I	75 (12.4)
IIA	175 (28.9)
IIB	31 (5.1)
IIC	23 (3.8)
IIIA	24 (3.9)
IIIB	151 (24.9)
IIIC	85 (14.04)
IVA	16 (2.6)
IVB	25 (4.1)
Hystopatologic result	
Adenocarcinoma	528 (87.3)
Mucinos adenocarcinoma	61 (10.1)
Signet cell carcinoma	16 (2.6)
Grading	
G1	120 (19.8)
G2	329 (54.3)
G3	156 (25.7)

Results

A total of 605 patients underwent surgery for colon cancer between January 1, 2013, and December 31, 2015. Demographic and clinical characteristics of the patients are listed in Table I. In this study group, 1-year mortality was 10.9%. Table II shows univariate analysis of patient characteristics in relation to 1-year mortality. 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 48U/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). Thus, age over 63 (p=0.01), the presence of cirrhosis (p=0.03), alcohol abuse (p=0.008) and urea levels > 48U/l influence 1-year mortality. Tumoral grading, TNM cancer stage, degree of colonic wall involvement (T), lymph node invasion (N), metastatic disease (M), lymphatic (L) and venous invasion (V) and tumoral resection margins (R) are factors that achieved statistical significance in relation to 1-year mortality after univariate analysis (Table III). Table IV shows the relationship between 1-year mortality and surgery-related factors. Type of surgery (elective or emergency), presentation with perforation of the colon (p=0.01) and multiorgan resections are the variables that influence 1-year mortality after colon cancer surgery. Following mul-

TABLE II - Univariate analysis of patient-related factors and 1-year mortality.

Variables	Deceasedn (%)	Survivorsn (%)	p
Gender	Female 30 (11.4)	231 (88.5)	0.69
	Male 36 (10.5)	308 (89.5)	
Age >63	73 (62; 79)	66 (58; 72)	0.01
Hemoglobin (g/dl)	10 (9; 11.5)	11 (10; 13)	0.73
Urea >48 U/l	57 (46; 80)	43 (29.5; 54.5)	0.005
Creatinine>1.19mg/dl	1.07(0.68;1.93)	0.93(0.75;1.12)	0.27
Total protein	6.9 (5.4;8)	7.2 (5.9;7.9)	0.41
Smoking	2 (7.2)	26 (92.8)	0.58
Alcohol	19 (19)	81 (81)	0.008
Ischemic heart disease	15 (9.7)	140 (90.3)	0.65
Kidney disease	2 (10.5)	17 (89.5)	0.95
Cirrhosis	3 (42.9)	4 (57.1)	0.03
Colorectal polyps	1 (3.9)	25 (96.1)	0.23
Colonic diverticulitis	5 (17.9)	23 (82.1)	0.22
Type II diabetes	8 (9.7)	75 (90.3)	0.068
Type I diabetes	1 (50)	1 (50)	0.07
History of surgical interventions	10 (11.3)	79 (88.7)	0.91
Associated neoplasms	5 (18.5)	22 (81.5)	0.19
ASA score	1 2 (6.9)	27 (93.1)	0.34
	2 28 (8.5)	300 (91.5)	
	3 12 (4.9)	236 (95.1)	
Blood loss (ml)	200 (150; 200)	200 (100; 300)	0.56
Resumption of transit (days)	Day 2 (2; 2.5)	Day 2 (2; 3)	0.79

TABLE III - Univariate analysis of tumor-related factors and 1-year mortality

Variables	Deceasedn (%)	Survivorsn (%)	p
Grading	G1 8 (6.9)	108 (93.1)	0.009
	G2 34 (10.8)	281 (89.2)	
	G3 18 (20.5)	70 (79.5)	
Stage	I 4 (5.06)	75 (94.93)	0.01
	IIA 3 (1.8)	172 (98.2)	
	IIB 0 (0)	31 (100)	
	IIC 3 (13.1)	20 (86.9)	
	IIIA 1 (4.2)	23 (95.8)	
	IIIB 17 (11.3)	134 (88.7)	
	IIIC 29 (45.4)	56 (54.6)	
	IVA 2 (12.5)	14 (87.5)	
	IVB 8 (32)	17 (68)	
T	T1 1 (4.9)	19 (95.1)	0.01
	T2 3 (4.1)	70 (95.9)	
	T3 20 (6.4)	294 (93.6)	
	T4 42(21.2)	156(78.8)	
N	N0 28 (5.7)	462 (94.3)	0.01
	N1 38 (38.8)	77 (61.2)	
M	M0 56 (9.93)	508 (90.07)	0.009
	M1 10 (34.3)	31 (65.7)	
Lymphatic invasion	L0 11 (3.3)	319 (96.7)	0.01
	L1 54 (19.6)	221 (80.4)	
Venous invasion	V0 36(7.2)	466(92.8)	0.01
	V1 29 (28.2)	74 (71.8)	
R	R0 40 (7.1)	530 (92.9)	0.01
	R1 13 (37.2)	22 (62.8)	
Ascending colon	33 (17.1)	161 (82.9)	0.002
Transverse colon	1 (7.7)	12 (92.3)	0.70
Descending colon	6 (8.8)	62 (91.2)	0.55
Sigmoid colon	26 (8.7)	273 (91.3)	0.08

TABLE IV - Univariate analysis of surgery-related factors and 1-year mortality.

Variables	Deceasedn (%)	Survivorsn (%)	p
Hospitalization type	Elective 44 (17.6)	453 (82.4)	0.001
	Emergency 22 (20.4)	86 (79.6)	
Reason for presentation			
occlusive colon tumor	13 (38.7)	58 (61.3)	0.05
Reason for presentation			
bowel perforation	6 (30)	14 (70)	0.01
Surgical approach	Laparoscopic 1 (2.5)	39 (97.5)	0.07
	Conventional 65 (11.5)	500 (88.5)	
Protective ileostomy	6 (17.7)	28 (82.3)	0.19
Preoperative mechanical			
bowel preparation	31 (8.8)	320 (91.2)	0.06
Multiorgan resection	17 (21.25)	63 (78.75)	0.003

TABLE V - Evaluation of independent risk factors for 1-year mortality

Variables	p	OR	95% CI
Age >63	0.01	2.05	1.16-3.62
Urea >48U/l	0.23	1.38	0.80-2.39
Alcohol abuse	0.01	2.058	1.17-3.61
Cirrhosis	0.25	2.025	0.59-6.89
Tumor grading (G)	0.09	4.23	0.79-6.18
Tumoral stage	0.03	3.10	1.10-8.75
Lymphatic invasion (L)	0.01	2.48	1.17-5.22
Venous invasion (V)	0.001	2.41	1.40-4.14
Resection margins (R)	0.18	1.51	0.81-2.81
Tumor location in the ascending colon	0.002	2.17	1.32-3.57
Emergency surgery	0.01	1.91	1.11-3.29
Multiorgan resection	0.01	2.07	1.15-3.74

tivariate analysis, 1-year mortality was significantly higher for patients age over 63 (OR 2.05), in case of alcohol consumption (OR 2.058), in case of advanced TNM stage (OR 3.10), lymphatic (L) OR 2.48 and venous (V) invasion (OR 2.41), after emergency surgery (OR 1.91), for tumors located in the ascending colon (OR=2.17) and after multiorgan resection (OR 2.07). The rest of the variables processed in the multivariate analysis did not achieve statistical significance (Table V).

Discussion

The aim of this study was to determine the impact of various patient, tumor and surgery-related factors over 1-year mortality rate for colon cancer patients that underwent radical surgery in a single, tertiary center. In the present study, 1-year mortality rate was 10.9%, percentage that is in the range found in literature of 8.5-14%^{3,7,11}. Multivariate analysis revealed that age over 63 years, alcohol abuse, advanced TNM stage, emergent surgery, tumors located in the ascending colon and multiorgan resections are risk factors for 1-year mortality after colon cancer surgery.

Older patients tend to have a higher risk of postoperative mortality. This aspect could rely on a low biological resource of the elderly or on a more advanced stage of the disease that is usually found at diagnosis⁷. Advanced age is not considered a contraindication in colon cancer surgery nowadays, but it must impose for a better postoperative surveillance and careful medical care. With the aging of the population, the number of cancer cases in elderly population will increase. It is estimated that by 2020 almost all cancer patients will be over the age of 65¹². Thus, a particular importance should be given to these patients regarding postoperative surveillance and care. More efforts should be directed towards a better understanding of the response of

these patients to surgical intervention. Nevertheless, knowledge, and respectively correction of factors that may influence their progression is essential to assure their best treatment.

The alcohol induced-carcinogenesis is well known in colon cancer¹³. Many literature studies have confirmed over time its role in the etiopathogenesis of the disease and admitted its role in post-operative unfavorable evolution¹³⁻¹⁴. Alcohol consumption is associated with post-operative complications like anastomotic leakage and high postoperative mortality rates¹⁴, even though according to some studies it does not influence 5-year survival¹⁵. Thus, alcohol consumption can have a role in delay recovery of the surgical patient and not necessary in the long-term evolution.

In a recent paper¹⁶, our study group also analyzed the impact of various factors on 30-day postoperative mortality after radical colon cancer surgery. According to the results obtained, emergent surgeries have a considerable negative impact on postoperative mortality, influencing both 30-day and 1-year mortality rates. Emergent surgeries are often performed for colon cancer complicated with either obstruction or perforation of the colon. Despite ongoing efforts to detect colon cancer in early stages, the rate of abovementioned complications is still high, between 15-40 %¹⁷, with a slight predominance of the obstructive complication¹⁷. Thus, emergent surgery, which has been shown to increase postoperative mortality, could be reduced by either avoiding or reducing complicated cases or by trying to treat them through non-surgical methods¹⁸. Self-expanding metallic stents have been proposed as a palliative treatment option in obstructive colon cancer, but according to the current European Society of Gastrointestinal Endoscopy¹⁹ and other recent studies²⁰⁻²¹, their use as "a bridge to surgery" is now also recommended. Their use would allow for better patient preparation and adequate tumoral staging before the elective surgery^{17,20-21}. Favorable results have been highlighted for both covered and non-covered stents²². It is thus mandatory to try to prevent late-stage, complicated presentations that may require emergent surgery. Properly applied screening programs could represent an adequate approach to reduce mortality in colon cancer patients and efforts must be made in this direction.

Postoperative mortality rate after multiorgan resection was higher compared with uncomplicated colon cancer resections, as shown before²³⁻²⁴, and a direct relationship was found between the number of resected organs and postoperative evolution of the patients²⁴. Intraoperative differentiation between inflammatory adhesions and tumor invasion is not possible, thus tumor dissection from surrounding structures is not recommended²⁵. Nevertheless, multiorgan resections remain the goldstandard treatment for advanced loco-regionally colon cancer patients and should always be performed when R0 resection can be achieved²⁵.

In the present study but also in other literature papers²⁶, 1-year postoperative mortality is higher after surgeries performed on the right colon compared with other localization, sustaining the idea of distinct disease with particular molecular mechanisms and chromosomal characteristics that differ from the rest of the colonic tumors²⁷. According to embryological origin of proximal (originates from midgut) and distal (originates from hindgut) colon cancers²⁸, the outcome differ in terms of postoperative outcomes²⁹, response to systemic chemotherapy³⁰ and overall survival³⁰⁻³¹. This aspects could lead to the need for a colon cancer subclassification and possibly to a separate study of the two entities.

In conclusion, even though colon cancer has been extensively studied for decades, we can not completely remove or prevent factors that influence postoperative mortality. So far, factors that influence postoperative mortality have been mostly studied up to 30 days postoperatively. But recent studies draw attention that the effect of factors influencing postoperative mortality extends up to 1-year after surgery. In this way, efforts must be directed to an appropriate surveillance of these patients and not least to a correct information of the patient regarding the existing risks.

Conclusions

Patients age over 63 with a history of alcohol consumption have a higher risk for 1-year postoperative mortality. Furthermore, advanced-stage colon tumors that oblige to emergent surgeries, tumors located in the ascending colon and multiorgan resections are characterized by an increased risk of death 1-year after colonic curative resections.

Riassunto

La gestione dei pazienti con cancro del colon rappresenta ancora oggi una sfida. Numerosi studi hanno evidenziato vari fattori che potrebbero avere un ruolo nell'evoluzione di questi pazienti dopo chirurgia radicale, ma è importante essere consapevoli con sufficiente certezza dei fattori che influenzano la mortalità postoperatoria di questa chirurgia. Però secondo alcuni studi recenti, riportare la mortalità postoperatoria a 30 giorni potrebbe offrire una sottostima del loro impatto sull'effettivo risultato postoperatorio.

Su questa premessa il presente studio ha analizzato l'impatto di vari fattori correlati a pazienti, tumori e chirurgia radicale in relazione alla mortalità ad 1 anno in pazienti con tumore del colon, facendo un confronto con i risultati ottenuti dallo stesso gruppo di studio in relazione a mortalità postoperatoria di 30 giorni. Mentre nessuna variabile correlata al paziente ha influenzato la mortalità a 30 giorni, l'età oltre i 63 anni e il consu-

mo di alcol hanno dimostrato di avere un impatto negativo sulla mortalità postoperatoria a 1 anno. I risultati di entrambi gli studi confermano che è fondamentale cercare di evitare interventi chirurgici in emergenza perché caratterizzati da un aumento dei tassi di mortalità alla scadenza di 30 giorni e di 1 anno.

La posizione del tumore del colon non influenza la mortalità postoperatoria a 30 giorni, ma i tumori del colon retto tendono ad avere una prognosi peggiore di 1 anno, come i tumori localmente avanzati sottoposti a resezione multiorgano. Complicazioni postoperatorie immediate, come emorragie o complicanze respiratorie condizionano maggiori probabilità di influenzare la mortalità precoce.

Vari fattori influenzano ancora la mortalità postoperatoria nei pazienti con cancro del colon, anche se l'evoluzione postoperatoria è favorevole. La conoscenza di questi fattori che potrebbero ulteriormente influenzare l'esito postoperatorio è importante per la sorveglianza postoperatoria e per un'accurata informazione sui rischi esistenti.

In particolare la riduzione della mortalità postoperatoria nella chirurgia del cancro del colon può essere ottenuta mediante cessazione del fumo, cercando di evitare interventi chirurgici in urgenza con la prevenzione delle fasi avanzate e complicate attraverso il miglioramento dei programmi di screening, con approccio possibilmente non chirurgico dei casi complicati, nel tentativo di preparare il paziente per un intervento chirurgico in elezione e per stadiare correttamente la situazione, ma anche riconoscendo l'importanza della localizzazione del tumore del colon e della loro gestione in base ai risultati noti.

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