Analysis of factors influencing early mortality in colorectal cancer surgery

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Abstract. Background and objectives: Tumor resection represents the main treatment in the complex management of patients with colorectal cancer; however, it can be hampered by significant morbidity and mortality. Early postoperative mortality is the result of an aggregate of factors that influence patient evolution. The aim of the study was to identify the predictive factors that lead to an increase in mortality in the first 30 postoperative days in colorectal cancer in Romania. Material and methods: The retrospective study included patients hospitalized over a period of 10 years, between 2004 and 2013, and who required colon or rectal resection for colorectal cancer. The following factors that might have influenced in-hospital and post-discharge postoperative mortality in the first 30 postoperative days were analyzed: age, gender, presence of anemia (Hgb<10 g dl-1) and insulin-dependent diabetes mellitus, admission criteria, elective or emergency operation, surgical approach and the characteristics of the tumor. Major postoperative complications such as occlusion, fistula and eviscerations were also analyzed. Results: The analysis included 510 patients. In the first 30 postoperative days 7.25% deaths were recorded: 5.88% deaths during hospital stay or after readmission and 1.4% deaths at home. The postoperative mortality is influenced by reinterventions ($p<0.0001$), postoperative anastomotic fistulas ($p<0.0001$) and postoperative intestinal occlusions ($p=0.005$). Age over 65 did constitute a significant risk factor for early mortality ($p=0.003$). Early mortality is not influenced by the timing of the surgery (emergency or elective) ($p=0.1243$), by the type of procedure (classical or laparoscopic) ($p=0.3456$), by anemia ($p=0.065$) or by diabetes mellitus ($p=1.87$). Conclusions: The results of the study outlined a group of patients with a higher risk of early postoperative death: patients over 60 years of age, patients with penetrating tumors and patients whose postoperative evolution required early reinterventions or was complicated by anastomotic fistulas and occlusions.

Key Words: early mortality, colorectal cancer

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Introduction

Colorectal cancer (CRC) represents a major public health issue (Ferlay et al 2013) and is the second most frequent cancer with respect to the number of new cases diagnosed in both Romania and other European countries (Siegel et al 2011).

Tumor resection represents the main treatment in the complex management of patients with this pathology; however, it can be hampered by significant morbidity and mortality. Early postoperative mortality (in the first 30 days) is considered an indicator for the efficiency of surgery services; studies published in the literature report an early mortality rate between 3.4% and 13.3% (Alves et al 2005; Faiz et al 2009).

Early postoperative mortality is the result of an aggregate of factors that influence patient evolution. A young person in the beginning stages of the disease, without any associated diseases will have a completely different risk compared to that of an elderly person, decrepit and in the later stages of the disease (Morris et al 2011). The timing of the operation (emergency or elective), the type of interventions and the complications that may arise (reinterventions, fistula, infections with various localizations, etc.) are added to patient characteristics. All of these factors may complicate the postoperative evolution of the patients, determining the increase of postoperative mortality and morbidity.

There are studies that had taken into consideration both the surgeon and the surgical services as a whole, finding that there is a decrease over time in postoperative mortality (Morris et al 2011), but an unexplained variation in mortality rates between different hospitals and geographical regions, too (Scootman et al 2014).The yearly number of patients undergoing operations for colorectal cancer varies between hospitals and surgeons as well. A recommendation to concentrate high-risk procedures into hospitals with a large volume of interventions has been outlined; this would lead to a decrease in postoperative mortality. The definitions used to describe a high-volume service are debatable, however (Weitz et al 2004). The results from a large population-based study (Karanicolas et al 2009) suggested that among surgeons carrying out a large number of colorectal resections, the rate of mortality is significantly inferior ($p=0.003$) than among surgeons with a low number of interventions, but that the size of the hospital has no influence over mortality.

The aim of the study was to identify the predictive factors that lead to an increase in mortality in the first 30 postoperative days in colorectal cancer in Romania.

Materials and methods

A retrospective analysis was carried out on the data of patients admitted in a 10-year period between January 2004 and December 2013; these could be found in patient records, electronic database of the surgery and morphopathology department database. We selected patients with colorectal cancer who underwent colic or rectal resection. The patients excluded from the study were those in need of relaparotomy, patients with other invasive abdominal cancers in the colon, patients undergoing exclusively transanal procedures and patients who had only undergone exploratory laparotomy, only internal derivation or only colostomy. After selection, a total of 510 patients were recruited in the study. Oral mechanical bowel preparation was prescribed for all patients having elective colorectal surgery. The patients were monitored for a period of 30 postoperative days. All patients included in the study signed the informed consent form and the study was approved by the Ethics Committee of the Mures Clinical County Hospital.

The following factors that might have influenced in-hospital and post-discharge postoperative mortality in the first 30 postoperative days were analyzed: age, gender, presence of severe or moderate levels of anemia (Hgb$<$10 g dl^{-1}), and insulin-dependent diabetes mellitus, admission criteria, elective or emergency operation, surgical approach and the characteristics of the tumor. Major postoperative complications that needed/didn't need reinterventions, such as occlusion, fistula and eviscerations, were also analyzed.

Statistical analysis of the data was performed using MedCalc program for statistics in biomedical research, SPSS version 17 or GRAPH Pad Prisma. We used Chi-square, Fisher, Student tests and multivariate regression analysis. The significance threshold widely accepted is 95% meaning P = 0.05.

Results

The final analysis included 510 patients who had undergone major procedures for colorectal cancer. In the first 30 postoperative days, 7.25% (n=37) deaths were recorded: 5.88% (n=30) deaths during hospital stay or after readmission and 1.4% (n=7) deaths at home.

The genders distribution in the operated cases was M/F=1.3/1 (289/221). Although the gender percentage distribution of deaths showed a predominance of males compared to females [9.0% (n=26) vs. 5.0% (n=11)], the values had no statistical significance (p=0.0878) [RR 1.807, CI 95% (0.9129 to 3.579); OR=1.887, CI 95% (0.9112 - 3.909)]. The average age of studied patients was 65 [64.87; min 33, max 89]. Of the 243 patients aged less than 65 years died 2.88% (n=7), compared with 11.2% (n=30) deaths that occurred in 267 patients over 65 years. Age over 65 did constitute a significant risk factor for early mortality (p=0.003) [RR=3.900, CI 95% (1.745 - 8.718); OR=4.268, CI 95% (1.838 - 9.909)].

We analyzed anemia and diabetes mellitus as risk factors for mortality in the first 30 postoperative days, and the results showed that these two variables have no influence on early deaths. The data obtained are shown in Table 1.

Emergency operations were carried out in 97 cases, while elective surgery was performed on 413 patients. 8.1% of the patients were operated using laparoscopic approach, whereas in 91.9%,

the open classical surgery was used. The results showed that early mortality is not influenced by the timing of the surgery (emergency or elective) (p=0.1243) [RR=1.801, CI 95% (0.9222 - 3.519); OR=1.904, CI 95% (0.9058 - 4.002)] or by the type of procedure (classical or laparoscopic) (p=0.3456)[RR=3.147, CI 95% (0.4426 - 22.38), OR=3.326, CI 95% (0.4439 - 24.91)]. In relation to the primary tumor, the group was consisted of 3.13% (n=16) T1, 14.9% (n=76) T2, 65.1% (n=332) T3 and 16.86% (n=86) T4. We made two different groups: T1+T2 vs. T3+T4. The analysis of two groups showed no significant correlation between the primary tumor and the early mortality (p=0.826) [RR=0.9433, CI 95% (0.4275 - 2.081); OD=0.9389, CI 95% (0.3990 - 2.209)]. TNM classification could be analyzed in 443 patients; the distribution of stages is shown in Table 2.

Table 1. Anemia and Diabetes mellitus in relation to early mortality

Characteristics of tumors		Number	Deaths	p
Anemia (g dl^{-1})	$<$10	161	17	0.065
	$>$10	349	20	
Diabetes mellitus	Present	8	2	0.87
	Absent	502	35	

The analysis of the location of the tumor (rectal or colonic) and of the characteristics the tumor (stenotic tumor, presence of clinical invasion into surrounding organs/tissues, presence of perforation, of ascites or distant metastases) is shown in Table 3. A statistical significance was found to exist between the tumor characteristics studied and mortality in the first 30 days only in the case of penetrating tumors, with a clinical presentation of infiltration into surrounding organs and tissues (p$<$0.05) (RR=2.005, CI 95% (1.071 - 3.752); OD=2.131, CI 95% (1.071 - 4.239)], while the other variables studied did not have a statistically significant influence on mortality.

We studied the relation between the immediate postoperative complications (early reinterventions, appearance of fistulas, eviscerations and occlusions) and the deaths in the first 30 days and. Out of the 44 patients who had undergone at least one early reintervention, 38.6% (n=17) deaths were recorded. The reinterventions increased the rate of early mortality by 46% (p$<$0.0001) (RR=9.002, CI 95% (5.101 - 15.89); OR=14.04, CI 95% (6.603 - 29.86)].

Eighteen of the 427 patients who had underwent colic or rectal resection followed by anastomosis developed postoperative anastomotic fistulas. Out of the patients with postoperative fistulas, 44% (n=8) had died in the first 30 postoperative days; the fistulas increased mortality by 21.6% (p$<$0.0001) [RR=6.991, CI 95% (3.699 - 13.21); OR=11.78, CI 95% (4.287 - 32.40)].

The postoperative evolution of patients with procedures done for colorectal cancer were complicated by eviscerations in 14 cases, with 7.1% (n=1) death recorded among these patients (p=1)[RR=0.9841, CI 95% (0.1450 - 6.680); OR=0.9829, CI 95% (0.1250 - 7.732)].

Postoperatively, 24 patients needed: reintervention (15) or intensive care (9) for intestinal occlusion, 25% (n=6) of these patients dying in the first 30 days (p=0.005) [RR=3.919, CI 95% (1.810 - 8.485); OR=4.892, CI 95% (1.812 - 13.21)]. Postoperative intestinal occlusion increased early mortality by 16.2%.

Table 2. TNM classification

	Stage 1	Stage 2a	Stage 2b	Stage 3a	Stage 3b	Stage 3c	Stage 4	N/A
Number	67	152	29	8	73	50	64	67
Deaths	4(5.97%)	12(7.89%)	2(6.89%)	0(0%)	3(4.1%)	5(10%)	8(12.5%)	3(4.4%)

Table 3. The analysis of the characteristics the tumor

Characteristics of tumors		Number	Deaths	p
Location of the tumor	Colon	305	27	0.116
	Rect	205	10	
Stenosis	Present	275	25	0.062
	Absent	235	12	
Penetration	Present	135	15	<0.05
	Absent	375	22	
Perforation	Present	58	2	0,415
	Absent	452	35	
Ascitis	Present	28	2	1
	Absent	482	35	
Metastasis	Present	64	8	0.115
	Absent	446	29	

Table 4. Multivariate analysis including demographic characteristics, comorbidities and type of surgery

Variables	Odds Ratio	95% CI	P
Gender	1.327	0.6531 to 2.6946	0.434
Age	4.160	1.7710 to 9.7736	0.001
Emergency vs Elective	1.842	0.8530 to 3.9755	0.12
Classical vs Laparoscopically	3.385	0.4405 to 26.0057	0.241
Diabetes mellitus	4.305	0.7603 to 24.3707	0.099
Ascites	1.088	0.2291 to 5.1663	0.916
Anemia	2.127	1.0552 to 4.2888	0.035

We used a multivariate regression analysis to indentify the variables that influenced the early postoperative mortality in colorectal cancer. The results are mentioned in tables 4 and 5.

Discussion

The studies published in the literature had analyzed several variables that might influence the postoperative evolution of patients operated on for colorectal cancer and that can lead to early death in the first 30 postoperative days. Our study retrospectively analyzed the influence of certain factors, including the characteristics of the patient and the tumors, as well as the development of postoperative complications.

We recorded a global early mortality rate of 7.25%; the data in the literature reports values ranging between 3.4 - 13.3% (Alves et al 2005, Faiz et al 2009). The data obtained during our study are comparable to those obtained by Morris et al (2011), who, analyzing 160,920 cases operated on by 150 surgical teams,

Table 5. Multivariate analysis including tumor characteristics and postoperative complications

Variables	Odds Ratio	95% CI	P
Anastomotic fistula	3.607	1.9127 to 14.2522	0.047
Colon vs Rect	0.502	0.2119 to 1.1873	0.117
Metastasis	3.182	1.2044 to 8.4042	0.020
Tumor penetration	2.120	1.9330 to 4.8154	0.043
Tumor perforation	0.3	0.0627 to 1.4355	0.132
Reintervention	13.281	5.2872 to 33.3579	<0.0001
Tumor stenosis	1.293	0.5702 to 2.9311	0.539
T1+T2 vs T3+T4	0.575	0.1943 to 1.7009	0.317

showed a 6.7% mortality resulting from major surgical resections. Similar percentages (7.5%) were obtained during a prospective descriptive study (Tekkis et al 2003) that analyzed 8,077 patients undergoing operations for colorectal cancer during a year in 73 hospitals.

Certain studies describe a higher mortality after emergency surgery (Panis et al 2011). Similarly, in our study, even in the absence of statistical significance, the mortality rate was higher in emergency operations than in elective surgery (11.3% vs. 6.3%). Similar results in elective surgery (6.2%) were reported in the Danish study carried out by Iversen (2012) on 23,222 patients operated on with a higher mortality rate after emergency interventions (21.1%).

In our study, age above 65 represents a statistically significant high risk factor involved in postoperative mortality (p=0.0003). A recent study on a large number of subjects (27,563) has also detected that age above 61 years represents an important risk factor in early deaths (Iversen et al 2014). The number of elderly patients with several comorbidities that required colorectal surgery has grown in the last decades: the number patients >74 years has increased from 19% to 29%, and the number of patients >84 years has doubled (from 3% to 6%), in a report carried out over 10 years (Nascimbeni et al 2009). In accordance with this trend, many studies had remarked on the fact that age over 70 years (Panis et al 2011) or even over 80 years (Morris et al 2011) represents a risk factor in early deaths. In our study, the average age of patients was 65 years, a comparatively lower age than that of patients from other populations studied: 76.5 years presented by Schneider (2012). In addition, more than half of the cases presented with advanced stages of illness (TNM 2b, 3 or 4), a fact that can be explained by the lack of a screening program for detecting colorectal cancer in our country and by late presentation, in advanced stages of the illness, even at younger ages, in Romania.

The articles that showed a decrease over time in the mortality in colorectal surgery attributed this reduction to an increase in the number of laparoscopic surgery; this approach represents an increasingly more widely used alternative to the classical open approach in elective colorectal surgery. The patients group undergoing laparoscopic surgery in our study was low (8.1%), yet there was only a single case of death (2.4% vs. 7.6%). Guillou (2005), in a randomized trial on 794 patients with colorectal cancer out of 27 hospitals, revealed similar mortality rates between classically (4%) and laparoscopically (5%) operated patients (p=0.57). Contrasting with the data mentioned above, a study performed over 10 years analyzed mortality at 30 and 365 days on 192,620 patients, of which 3,709 (1.9%) were operated laparoscopically, and the results showed that patients operated laparoscopically had a lower early mortality rate at 1 year as well, as compared to open surgery (p<0.05) (Faiz et al 2009). Similar results were quoted by Mamidanna (2012), who showed lower rated of mortality after laparoscopic interventions (p< 0.001). The same statistical significance in reducing early mortality by employing laparoscopic surgery was obtained in the study reported by Panis (p< 0.001) (2011).

Tumors penetrating adjacent structures require complex surgical procedures performed to achieve complete excision; these interventions have a high risk of complications, including death. In a study comprising patients with locally advanced stages of colorectal cancer, Lehnert reported an early mortality rate of 7.5%; the deaths occurred via septic, hemorrhagic or medical complications. In these patients, the mortality rate was higher in colon cancer than in rectal cancer (9.4% vs. 3.2%; p=0.016) and higher in emergency surgery than in elective surgery (22% vs. 5.2%; p=0.007) (Lehnert et al 2002). Our data showed that locally advanced colorectal tumors, with signs of infiltration into surrounding structures and organs, had a statistical impact on early postoperative mortality by p<0.05.

Several studies showed an important correlation between reinterventions and postoperative mortality, suggesting that complications requiring surgical reinterventions are associated with an increased risk of death. Morris (2007) analyzed 26,638 patients with colorectal cancer, of which 1,558 (5.8%) required at least one reintervention in the first 30 days after colorectal resection. Early mortality was 10.5% in patients requiring one reintervention and 28.2% in patients requiring two or more reinterventions. The relative risk of early mortality in these patients was 7.2 [CI 95% (5.1 - 9.7)]. In accordance with the data presented, in our study, 17 of the 37 deaths occurred in patients requiring reinterventions; early mortality was significantly higher in association with early reoperations (p<0.0001).

One of the severe complications that occur after colorectal surgery is anastomotic leakage, associated with a significant increase in early mortality (10% in patients with fistulas vs. 2% in the group without fistulas; p=0.014) (Branagan et al 2005). In our study, anastomotic leaks were significantly associated with early mortality, 8 out of the 44 patients with anastomotic fistulas dying in the first 30 postoperative days (p<0.0001). The analysis of early mortality related to the stage of the disease showed an increase simultaneously with the progression of the disease from 5.97% (stage I) to 12.5% (stage IV), although without being statistically significant.

Conclusions

The results of the study outlined a group of patients with a higher risk of early postoperative death: patients over 65 years of age, patients with penetrating tumors and patients whose postoperative evolution required early reinterventions or was complicated by anastomotic fistulas and occlusions.

References

Alves A, Panis Y, Mathieu P et al. Postoperative mortality and morbidity in French patients undergoing colorectal surgery: results of a prospective multicenter study. Arch Surg 2005;140(3):278.

Branagan G, Finnis D.Wessex. Colorectal Cancer Audit Working Group. Prognosis after anastomotic leakage in colorectal surgery. Dis Colon Rectum 2005;48(5):1021-1026.

Faiz O, Warusavitarne J, Bottle A, Tekkis PP, Darzi AW, Kennedy RH. Laparoscopically assisted vs. open elective colonic and rectal resection: a comparison of outcomes in English National Health Service Trusts between 1996 and 2006. Dis Colon Rectum 2009;52(10):1695-704.

Faiz O, Warusavitarne J, Bottle A, Tekkis PP, Clark SK, Darzi AW, Aylin P. Nonelective excisional colorectal surgery in English National Health Service Trusts: a study of outcomes from Hospital Episode Statistics Data between 1996 and 2007. J Am Coll Surg 2010;210(4):390-401.

Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, CoeberghJ.W.W, Comber H, Forman D, Bray F. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries in 2012. European Journal of Cancer 2013;49; 1374-1403.

Guillou PJ, Quirke P, Thorpe H, Walker J, Jayne DG, Smith AM, Heath RM, Brown JM; MRC CLASICC trial group. Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre,randomised controlled trial. Lancet 2005;365(9472):1718-26.

Iversen LH. Aspects of survival from colorectal cancer in Denmark. Dan Med J 2012;59(4):B4428.

Iversen LH, Ingeholm P, Gögenur I, Laurberg S. Major reduction in 30-day mortality after elective colorectal cancer surgery: a nationwide population-based study in Denmark 2001-2011. Ann SurgOncol 2014;21(7):2267-73.

Karanicolas PJ, Dubois L, Colquhoun PH, Swallow CJ, Walter SD, Guyatt GH. The more the better?: the impact of surgeon and hospital volume on in-hospital mortality following colorectal resection. Ann Surg 2009;249(6):954-9.

Lehnert T, Methner M, Pollok A, et al. Multivisceral resection for locally advanced primary colon and rectal cancer: an analysis of prognostic factors in 201 patients. Ann Surg 2002;235:217–225.

Mamidanna R, Burns EM, Bottle A, Aylin P, Stonell C, Hanna GB, Faiz O. Reduced Risk of Medical Morbidity and Mortality in Patients Selected for Laparoscopic Colorectal Resection in England. A Population-Based Study FREE Arch Surg 2012;147(3):219-227.

Morris AM, Baldwin LM, Matthews B, Dominitz JA, Barloe WE, Dobie SA, Billingsley KG. Reoperation as a Quality Indicator in Colorectal Surgery.A Population-Based Analysis. Ann Surg 2007;245(1):73–79.

Morris EJA, Taylor EF, Thomas JD, Quirke P, Finan PJ, Coleman MP, Rachet B, Forman D. Thirty-day postoperative mortality after colorectal cancer surgery in England. Gut 2011;60:806-813.

Nascimbeni R, Di Fabio F, Di Betta E, Salerni B. The changing impact of age on colorectal cancer surgery.A trend analysis. Colorectal Dis 2009;11:13-8.

Panis Y, Maggiori L, Caranhac G, Bretagnol F, Vicaut E. Mortality after colorectal cancer surgery: a French survey of more than 84,000 patients. Ann Surg 2011;254(5):738-43.

Scootman M, Lian M, Pruitt SL, Hendren S, Mutch M, Deshpande AD, Jeffe DB, Davidson NO. Hospital and Geographic Variability in Two Colorectal Cancer Surgery Outcomes: Complications and Mortality After Complications. Ann SurgOncol 2014;21(8):2659-66

Schneider EB, Hyder O, Brooke BS, Efron J, Cameron JL, Edil BH, Schulick RD, Choti MA, Wolfgang CL, Pawlik TM. Patient readmission and mortality after colorectal surgery for colon cancer: impact of length of stay relative to other clinical factors. J Am Coll Surg 2012;214(4):390-8.

Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin 2011;61:212–236.

Tekkis PP, Poloniecki JD, Thompson MR, Stamatakis JD. Operative mortality in colorectal cancer: prospective national study. BMJ 2003;327(7425):1196.

Weitz J, Koch M, Friess H, Büchler MW. Impact of volume and specialization for cancer surgery. Dig Surg 2004;21(4):253-61.

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