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Nonelective Left-Sided Colon Cancer Resections are Associated with Worse Postoperative and Oncological Outcomes: A Propensity-Matched Study

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Rezumat

Rezecțiile non-elective pentru cancerul de colon stâng sunt asociate cu rezultate postoperatorii și oncologice nefavorabile: un studiu propensity-matched

Introducere: Pacienții cu o intervenție chirurgicală în regim de urgență au un risc considerabil mai ridicat de a dezvolta complicații postoperatorii și prezintă o mortalitate mai mare comparativ cu cei operați electiv. Deși contrazisă de unele studii, dovezile actuale susțin că pacienții cu intervenții colorectale în urgență prezintă o rată semnificativ mai mare a complicațiilor postopertorii și rezultate oncologice nefavorabile.

Metodă: Am inclus în acest studiu toți pacienții cu cancer de colon internați în Spitalul Clinic de Urgență București în perioada Ianuarie 2011 – Ianuarie 2016. Criteriile de selecție au fost: (1) tumora colonică; (2) localizare la nivelul colonului stâng; (3) adenocarcinom la examenul histopatologic. Criterii de excludere: (1) cancer rectal; (2) patologie benignă (ex. diverticulita).

Rezultate: Au fost incluşi 615 pacienți cu cancer de colon stâng. 275 (44.7%) dintre pacienți s-au prezentat cu boală malignă complicată. Complicațiile au fost reprezentate de obstrucție la 205 (33.3%) pacienți (GO), hemoragie la 55 (8.9%) pacienți (GH) și perforație la 15 (2.4%) pacienți (GP). Rata de fistulă anastomotică a fost similară la cei din grupul cu obstrucție cu cei operați electiv (6.2% versus 6.5%, P>0.05), dar a fost semnificativ mai mare pentru pacienții cu hemoragie (16%) (P=0.046). Rata de complicații și

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mortalitatea la 30 de zile au fost semnificativ mai mari la pacienții operați în regim urgență (P<0.05).

Concluzii: Prognosticul pe termen scurt și cel pe termen lung a fost nefavorabil pentru pacienții operați non-electiv pentru cancer de colon stâng. Corelând prognosticul rezervat cu rata de incidență crescută a bolii complicate, putem reafirma impactul semnificativ al malignitații colonice complicate în populația generală.

Cuvinte cheie: cancer de colon, complicație, chirurgie de urgență

Abstract

Background: Emergency general surgery patients are at significant risk of postoperative complications and mortality compared with their elective counterparts. Although challenged by some studies, increasing evidence shows that emergency colectomy for cancer is associated with worse early postoperative and long-term outcomes.

Methods: We have included all patients with colon cancer admitted to the Emergency Hospital of Bucharest between January 2011 and January 2016. Selection criteria: (1) colon tumor; (2) left-sided localization of the tumor; (3) pathology exam revealing adenocarcinoma. Exclusion criteria: (1) rectal cancers; (2) benign pathology (e.g. diverticulitis).

Results: We included 615 patients with left-sided colon cancer. 275 (44.7%) patients presented complicated disease. The complication was represented by obstruction in 205 (33.3%) patients (OG), hemorrhage in 55 (8.9%) patients (HG), and perforation in 15 (2.4%) patients (PG). The anastomotic leakage rate was similar between obstructive and elective cases (6.2% versus 6.5%, P>0.05), but was significantly higher for hemorrhagic patients (16%) (P=0.046). The 30-day complication rate and mortality were significantly higher in emergency patients (P<0.05).

Conclusions: We found significant worse short- and long-term outcomes for patients with non-elective left-sided colon cancer resections. Correlating the ominous prognosis with the high incidence of the complicated disease, we may emphasize the impact on de complicated colon cancer on the general population.

Key words: colon cancer, complicated disease, emergency surgery

Introduction

Emergency general surgery patients are at significant risk of postoperative complications and mortality compared with their elective counterparts (1,2). Although challenged by some studies (3), increasing evidence shows that emergency colectomy for cancer is associated with worse early postoperative and long-term outcomes (4-6).

Analysis of colorectal cancer survival showed an increasing 30-day survival, from 86% (time interval 1977 - 1982) to 90% (time interval 1995 - 1999) for colon cancer and from 90% to 94% for rectal cancer (7). Nevertheless,

the emergency surgery for colon and rectal cancers was associated with a pooled 30-day mortality of 22.1%, significantly higher than 6.2% for elective patients (7). On the other hand, the emergency presentation was associated with poorer overall survival even in node negative patients with curative intent surgery (5-year overall survival 66.8% versus 91.8%, P < 0.001) (6).

The necessity for direct research and quality improvement audits was underlined by a national cohort study coming from the United Kingdom, which showed that outliers hospitals regarding mortality after elective and nonelective colorectal surgery do not correlate closely (8). Analysis of Nationwide Inpatients Sample from the United States revealed significant state-by-state variation in emergency colectomies (9). After inclusion of 203050 patients, the authors found the highest proportion of emergent procedures in Nevada (53.6%) and the lowest in Texas (22.8%) (9). Besides the detrimental impact on patients' outcomes, the emergency surgery is also associated with incremental costs, with \$8741.22 (53%) increase) in colon resections (10). Proposed measures to improve the disease specific survival in patients with emergency colon resections maybe a more extended lymph node assessment, better follow-up, and better utilization of adjuvant chemotherapy (11). Public healthcare policies, such as colorectal cancer screening, seems to decrease the rate of emergency resections and to save lives (12). Description of populational groups at high risk for developing complicated colorectal cancer, such as older, socially deprived and ethnic minority patients (12) could improve survival outcomes for colorectal cancer.

The implications of colon cancer diagnosis after the emergency presentation are underresearched, with a wide heterogeneity throughout the literature regarding the definition of emergency cases and patients' inclusion criteria (13).

The objective of this article is to evaluate the short-term perioperative morbidity and the long-term oncological outcomes of patients with nonelective left-sided colon cancer, comparing them with those of elective patients.

Methods

Patients

We have included all patients with colon cancer admitted to the Emergency Hospital of Bucharest between January 2011 and January 2016. Selection criteria: (1) colon tumor; (2) left-sided localization of the tumor; (3) pathology exam revealing adenocarcinoma. Exclusion criteria: (1) rectal cancers; (2) benign pathology (e.g. diverticulitis). We have defined as complication the diagnosis of an

obstructive, hemorrhagic, or perforated tumor, without using a cutoff value for the time interval between admission and operating room.

Variables

We extracted the following data: patients' demographics, status on admission (emergency or not), TNM stage of the disease, pre-existing co-morbidities, overall survival, hospital stay, anastomotic leakage, postoperative complications according to Clavien-Dindo scale, surgical data (surgical approach, presence of loop ileostomy, on-table lavage, type of colon resection, type of anastomosis, duration of surgery), postoperative treatment, blood samples, pathology exam of the resection specimen. We have divided the patients into nonelective (complicated) and elective (un-complicated) groups.

Primary Outcome

The primary outcome of the present study was the overall survival, defined as the time interval between surgical procedure and death.

Secondary Outcomes

The secondary outcomes include the 30-day complication rate.

Statistical Analysis

We presented the continuous variable as mean and standard deviation and the categorical variables as number and percentages. We have used Chi-square tests, Independent Samples T-Test, One-Way ANOVA as statistical tests, where appropriate. For survival analysis, we used Kaplan-Meier analysis and Long Rank (Mantel-Cox) test. We performed propensity score matching, using as covariates the TNM stage and the age of patients. We used a match tolerance of 0.25. 270 matches were obtained. The incremental rejection percentage was 71.199.

For statistical analysis, we have used Statistical Package for Social Sciences (SPSS) version 20 and R Statistical Software version 3.4.1. To claim statistical significance, we used a P<0.05.

Results

We included 615 patients with left-sided colon cancer. 275 (44.7%) patients presented complicated disease (see *Table 1*). The complication was represented by obstruction in 205 (33.3%) patients (OG), hemorrhage in 55 (8.9%) patients (HG), and perforation in 15 (2.4%) patients (PG). The mean age was 66.07±12.52

years in complicated patients (CG) and 67.63±11.04 in elective cases (EG) (P=0.102). There was no difference in sex distribution between the groups, male representing 120 (58.5%), 30 (54.5%), 10 (66.7%), and 190 (55.9%) of cases in obstructing, hemorrhage, perforation, and elective groups (P Chi-square Tests > 0.05). Patients with complicated disease presented more advanced TNM stages (see *Table 2*). The hospital stay was significantly longer for emergency cases (11.55±3.91 versus 7.5±2.05 days, P<0.001). Emergency surgery was

Table 1. Characteristics of the included patients

Variable	Group	Data (number and percentages or mean and standard deviation)	Statistical significance			
Complication	Obstruction	205 (33.3%)				
	Hemorrhage	55 (8.9%)				
	Perforation	15 (2.4%)				
	Elective	340 (55.3%)				
Sex (Male)	Obstruction	120 (58.5%)	P Chi-square Tests > 0.05			
	Hemorrhage	30 (54.5%)				
	Perforation	10 (66.7%)				
	Elective	190 (55.9%)				
Age (years)	Obstruction	64.85±13.72	- P Post Hoc Tests Hemorrhage vs.			
	Hemorrhage	70.54±6.57	Obstruction=0.008			
	Perforation	66.33±7.62	- P Post Hoc Tests Obstruction vs.			
	Elective	67.63±11.04	Elective=0.043			
Hospital stay	Obstruction	11.72±4.50	- P Post Hoc Tests Obstruction vs.			
(days)	Hemorrhage	10.98±1.08	Elective < 0.001			
,	Perforation	11.47±1.18	- P Post Hoc Tests Hemorrhage vs.			
	Elective	7.5±2.03	Elective < 0.001 - P Post Hoc Tests Perforation vs. Elective < 0.001			
Anastomotic	Obstruction	9 (6.2%)	P Chi-Square Tests = 0.046			
leakage	Hemorrhage	8 (16%)	·			
	Elective	20 (6.5%)				
Anastomotic	Emergency	17 (8.7%)	P Fischer's Exact Test = 0.341			
leakage	Elective	20 (6.5%)				
Anastomotic	Yes	Age = 80.33±8.08	P Independent Samples T-Test,			
leakage	No	Age=68.54±10.16	Bootstrap=0.001			
Anastomotic	Yes	Hemoglobin on admission	P Independent Sample T-Test,			
leakage		= 13.19±1.56	Bootstrap=0.009			
	No	Hemoglobin on admission				
		= 11.70±3.09				
Anastomotic	TNM Sage I	0 (0%)	P Chi-Square Tests=0.001			
leakage (Yes)	TNM Sage II	0 (0%)	·			
J , ,	TNM Sage III	24 (11%)				
	TNM Sage IV	13 (9.9%)				

Table 2. Correlation between the emergency patients and TNM stage of the disease.

			Emergency	
			Yes	No
TNM Stage	Stage I	Count	0 _a	30 _b
		% within TNM stage	0,0%	100,0%
		% of Total	0,0%	5,0%
	Stage II	Count	30 _a	105 _b
		% within TNM Stage	22,2%	77,8%
		% of Total	5,0%	17,6%
	Stage III	Count	147 _a	115 _b
		% within TNM stage	56,1%	43,9%
		% of Total	24,7%	19,3%
	Stage IV	Count	93 _a	75 _b
		% within TNM Stage	55,4%	44,6%
		% of Total	15,6%	12,6%

associated with a significantly higher rate of total/subtotal colectomies and Harmann's type resections (see *Table 3*). The anastomotic leakage rate was similar between obstructive and elective cases (6.2% versus 6.5%, P>0.05), but was significantly higher for hemorrhagic patients (16%) (P=0.046). The anastomotic leakage rate correlates with the patients' age (80.33±8.08 versus 68.54±10.16, P=0.001), lower hemoglobin (13.19±1.56 versus 11.70±3.09, P=0.009), and advanced disease stage (P=0.001).We found no association

between diabetes mellitus, cardiovascular morbidities, respiratory pre-existing morbidities and anastomotic leakage rate (P>0.05) (see $Table\ 4$). The 30-day complication rate and mortality were significantly higher in emergency patients (P<0.05) (see $Table\ 5$). Emergent surgery was associated with a higher reintervention rate (P = 0.018). The R1/R2-type resections were more frequent in nonelective patients (OR = 2.308, 95% CI 2.106 to 2.529). The overall survival was significantly worse for emergency cases, with an odds ratio of 1.702 (95%

Table 3. Correlation of the emergency status with the surgical procedure

		Emergency		Total
		Yes	No	
Surgical resection	Left hemicolectomy	85 _a	165 _b	250
· ·		34,0%	66,0%	100,0%
	Total/subtotal colectomy	29a	0b	29
		100,0%	0,0%	100,0%
	Hartmann's type	46 _a	5 _b	51
		90,2%	9,8%	100,0%
	Sigmoidectomy	110 _a	135 _a	245
		44,9%	55,1%	100,0%
	Resection of the splenic angle	15 _a	10 _a	25
		60,0%	40,0%	100,0%

Each subscript letter denotes a subset of Emergency categories whose column proportions do not differ significantly from each other at the 0.05 level.

Table 4. Preexisting co-morbidities impact on anastomotic leakage rate

Co-morbidity	Odds Ratio	95% Confidence Interval
Diabetes mellitus (Yes/No)	1.397	0.554-3.518
Cardiovascular diseases (Yes/No)	1.670	0.767-3.634
Respiratory diseases (Yes/No)	1.459	0.477-4.461

Confidence Interval 1.373 to 2.109) (see *Table 6* and *Fig. 1*). Subgroup analysis of the overall survival according to the patients' gender showed a worse survival in male patients for elective cases (OR = 0.809, 95% CI 0.712 to 0.919), but nor in emergent surgeries (OR = 0.907, 95% CI 0.727 to 1.130). Patients with perforated tumors presented the worse overall survival (see *Table 7* and *Fig. 2*). After propensity score matching, the emergency surgery was also associated with worse overall survival (see *Fig. 3*).

Discussions

The present study revealed significant worse short- and long-term outcomes for patients with complicated left-sided colon cancer.

There is evidence that women have longer adjusted survival compared with men (14), although they present more frequent as emergencies, and at older ages (HR = 0.91, P < 0.001) (15). In our study, we found a gender

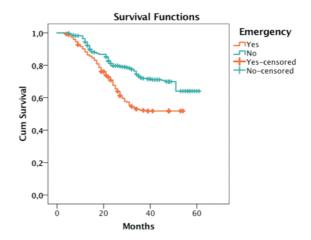


Figure 1. Kaplan-Meyer analysis for Overall Survival of emergency versus elective colon cancer resections (P Long Rank (Mantel-Cox)<0.001).

effect, with better overall survival in women, in elective cases, but not in emergent ones.

Although controversial, the laparoscopic approach may be used for selected cases, with similar 3-year overall survival rate, 3-year recurrence free survival rate, lymph node harvesting and shorter hospital stay (16). In our cohort, including only emergency patients, the emergency laparoscopic approach was used in 3.6% of patients.

According to Danish Colorectal Cancer Group Database, the postoperative mortality after emergency colonic resections for cancer was 22%, while in patients who develop medical

Table 5. Correlation between postoperative morbidity according to Clavien-Dindo Scale and type of colon cancer complication

			Postoperative Complications Clavien Dindo Class						Total
			I	II	III	IV	V	No	
Complication	Hemorrhage	Count	9 _a	4 _a	5 _b	1 _a	0 _a	36 _a	55
of the disease		% within Complication of the disease	16,4%	7,3%	9,1%	1,8%	0,0%	65,5%	100,0%
	Perforation	Count	0_a	4 _{b. c}	0 _{a, b, c}	1 _{a, c}	5 _b	5 _a	15
		% within Complication of the disease	0,0%	26,7%	0,0%	6,7%	33,3%	33,3%	100,0%
	Obstruction	Count	32 _a	10 _a	3 _a	10 _a	5 _a	145 _a	205
		% within Complication of the disease	15,6%	4,9%	1,5%	4,9%	2,4%	70,7%	100,0%
	Elective	Count	41 _{a, b}	11 _b	0 _c	11 _{a, b}	6 _{a, b}	271 _a	340
		% within Complication of the disease	12,1%	3,2%	0,0%	3,2%	1,8%	79,7%	100,0%
Total		Count	82	29	8	23	16	457	615
		% within Complication of the disease	13,3%	4,7%	1,3%	3,7%	2,6%	74,3%	100,0%

Each subscript letter denotes a subset of Postoperative Complications Clavien Dindo Class categories whose column proportions do not differ significantly from each other at the 0.05 level.

 Table 6.
 Overall survival of patients with emergency versus elective colon cancer surgery

	Risk Estimate		
	Value		nfidence rval
		Lower	Upper
Odds Ratio for Emergency (Yes / No)	,432	,309	,605
For cohort Survival = Yes	,736	,647	,836
For cohort Survival = No	1,702	1,373	2,109
N of Valid Cases	615		

complications was as high as 57.8% (7,17). The anastomotic leak significantly worsens not only on the early postoperative results but is associated with increased distant recurrence rate (HR = 1.42, 95% CI 1.13 to 1.78) and long-term all-cause mortality (HR = 1.20, 95% CI 1.01 to 1.44)(18). These maybe partially explained by canceled of delayed chemotherapy administration (18). In our patients, the emergency surgery was not associated with an increased risk of anastomotic leakage in obstructive lesions, but this was significantly higher in hemorrhagic patients. However, should be noted that in obstructive lesions, the proportion of Hartmann's type resections, and total/subtotal colectomies was significantly higher than in elective patients.

The Dutch Surgical Colorectal Audit showed 5934 (19.2%) out of 30907 patients with non-elective colonic resection managed between 2009 and 2013 (19). The mortality was significantly higher after non-elective procedures (8.5% versus 3.4%, P<0.001). After emergency procedures, the right-sided tumors and anastomotic leakage were prognostic factors for high mortality (19). For elderly patients (more than 80 years) with an American Society of

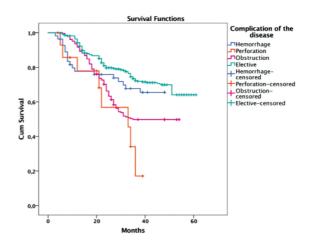


Figure 2. Kaplan-Meyer analysis for Overall Survival of emergency (with subgroups according to the complication type) versus elective colon cancer resections.

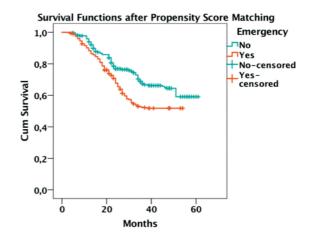


Figure 3. Kaplan-Meyer analysis for Overall Survival of emergency (with subgroups according to the complication type) versus elective colon cancer resections (P Long Rank (Mantel-Cox)=0.001).

Anesthesiology score equal or higher than III and a left hemicolectomy in non-elective setting, the

Table 7. Log rank (Mantel-Cox) pairwise comparison for Overall Survival of emergency (with subgroups according to the complication type) versus elective colon cancer resections.

Pairwise Comparisons									
	Complication Hemorrhage Perforation Obstruction Elective								
	of the disease	Chi-Square	Sig.	Chi-Square	Sig.	Chi-Square	Sig.	Chi-Square	Sig.
Log Rank (Mantel-Cox)	Hemorrhage			3,673	0,055	2,446	0,118	1,330	0,249
	Perforation	3,673	0,055			1,755	0,185	12,413	0,000
	Obstruction	2,446	0,118	1,755	0,185			22,313	0,000
	Elective	1,330	0,249	12,413	0,000	22,313	0,000		

postoperative mortality is 41%, significantly higher than 7% for patients without additional morbidities (20).

An investigation of the 11-year practice of emergency colorectal surgery in the United Kingdom, including 102236 patients, revealed a 30-day in-hospital mortality of 13.3% for colorectal cancer and 15.4% for diverticular disease (21). The 1-year postoperative mortality was 34.7% and 22.6%, respectively (21). Mamidanna et al. evaluated all patients over 70 years who underwent nonelective colorectal resections in English National Health Service Trust hospitals between 2001 and 2008 (22). 30day mortality was 17%, 23.3%, and 31% for patients aged 70-75, 76-80, and > 80 years old (P < 0.001). The reoperation rate was 6.3%, and the overall 30-day medical complication rate was 33.7%. The 1-year postsurgical mortality was 51.2% in patients over 80 years old (22). In our study, emergency patients presented a higher postoperative overall morbidity, severe complication, and mortality rate.

Analysis of 473619 surgical procedures from 198 hospitals included in the American College of Surgeons National Surgical Quality Improvement Program, revealed that emergency general surgery procedures are associated with increased overall morbidity (OR = 1.20, P < 0.05), serious morbidity (OR = 1.26, P < 0.05), and mortality (OR = 1.39, P < 0.05)(1). Aguina et al. underlined the public health burden represented by the nonelective colon cancer resections (5). They published the results of 26420 colon cancer patients included in the New York State Cancer registry and Statewide Planning and Research Cooperative System. 26.5% of patients were operated in emergency conditions, and were associated with increased 30-day mortality (OR = 3.42, 95% CI 2.87 to 4.06), stoma creation (OR = 4.49, 95% CI 3.95 to 5.09), discharge to another healthcare facility (OR = 2.46, 95% CI 2.26 to 2.68), worse disease specific (hazard ratio – HR = 1.74, 95% CI 1.61 to 1.88) and overall survival (HR = 1.64, 95%CI 1.55 to 1.75) (5). Analysis of the 214174 colectomies, defined as those performed during the first 24 hours from admission, from National Cancer Database revealed that 30% were performed in emergency conditions. Analysis of 30685 patients

from the Surveillance, Epidemiology and End Results database showed a five-year disease specific survival of 86.3% and 75.4% of elective and emergency colon cancer resections, respectively (11). However, an important proportion of these differences were explained by more advanced tumor stages and preexisting comorbidities in patients with non-elective resections (11). Although inferior long-term survival is associated with emergency surgery and inappropriate lymphadenectomy, the lymph node harvest seems to be similar between emergent and elective colon resections (23). In our study, we found a higher rate of R1/R2-type resections in emergent cases.

All the outcomes of patients with colon cancer seems to be improved by their management from high volume surgeons (24, 25): the postoperative mortality is lower (OR = 0.75, 95% CI 0.62 to 0.92), better 5-year overall survival (OR = 1.14, 95% CI 1.08 to 1.20), and lower anastomotic leakage rate (OR 0.64, 95% CI 0.40–1.02) (24). Due to technical challenges and high complication rate associated with emergency colectomies, we may assume the necessity of highly experienced surgeons for patients with complicated disease. A comparison of hospital performance in trauma versus emergency and elective general surgery revealed a significantly better processes organization and quality of care for trauma patients than for general emergency procedures (26).

The results of the present study should be considered in light of several limitations, especially due to its retrospective nature. First, a major limitation of the current research is the heterogeneity of patients defined as emergency cases. Second, there was a relatively low number of perforated tumors, which were associated with a significantly lower short- and long-term outcomes than the other two complications. However, using propensity score matching we diminished the impact of heterogeneity between the groups, but these were not repealed.

Conclusions

The present study revealed significant worse short- and long-term outcomes for patients with nonelective left-sided colon cancer resections. Correlating the ominous prognosis with the high incidence of the complicated disease, we may emphasize the impact on de complicated colon cancer on the general population.

Conflict of Interests

The authors declare no conflict of interests.

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