

BRIEF ARTICLE

Impact of age-related comorbidity on results of colorectal cancer surgery

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Abstract

AIM: To analyze the correlation between preexisting comorbidity and other clinicopathological features, short-term surgical outcome and long-term survival in elderly patients with colorectal cancer (CRC).

METHODS: According to age, 403 patients operated on for CRC in our department were divided into group A (< 70 years old) and group B (\geq 70 years old) and analyzed statistically.

RESULTS: Rectal localization prevailed in group A (31.6% vs 19.7%, $P = 0.027$), whereas the percentage of R0 resections was 77% in the two groups. Comorbidity rate was 46.2% and 69.1% for group A and B, respectively ($P < 0.001$), with a huge difference as regards cardiovascular diseases. Overall, postoperative morbidity was 16.9% and 20.8% in group A and B, respectively ($P = 0.367$), whereas mortality was limited to group B (4.5%, $P = 0.001$). In both groups, patients who suffered from postoperative complications had a higher overall comorbidity rate, with preexisting cardiovascular diseases prevailing in group B ($P = 0.003$). Overall 5-year survival rate was significantly better

for group A (75.2% vs 55%, $P = 0.006$), whereas no significant difference was observed considering disease-specific survival (76.3% vs 76.9%, $P = 0.674$).

CONCLUSION: In spite of an increase in postoperative mortality and a lower overall long-term survival for patients aged \geq 70 years old, it should be considered that, even in the elderly group, a significant number of patients is alive 5 years after CRC resection.

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Key words: Colorectal cancer; Elderly; Post-operative complications; Co-morbidity; Aged

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INTRODUCTION

Colorectal cancer (CRC) generally is considered a disease of the elderly^[1] because of its rising incidence with age^[2-6]. It represents an important cause of morbidity and mortality in the elderly population^[1], which mainly undergo emergency surgery because of bowel obstruction or perforation^[1,2,7-9]. Several authors have reported that elderly patients with CRC can be treated by standard surgical resection and surgery should not be denied on account of chronological age^[1,3,8,10,11]. Comorbidity, previously different tumors, and poor performance status represent the early and late negative prognostic factors in elderly patients^[1,2,7,10,12-15]. The purpose of this observational study was to evaluate our experience with CRC, to assess surgical and prognostic features of patients aged \geq 70 years compared with younger patients, with special reference to related comorbidity.

MATERIALS AND METHODS

Population under study

Between January 1999 and March 2006, 420 patients with CRC were observed in our department. Among these, seven patients were not operated on because of their poor general status or advanced stage of disease, and 10 patients were lost at follow-up. Thus, 403 patients (229 male and 174 female) with a mean (\pm SD) age of 67.2 ± 11.5 years (range 23–98 years) were analyzed retrospectively. According to the age at operation, two groups were considered: group A (< 70 years old; 225 patients) and group B (≥ 70 years old; 178 patients).

Preoperative assessment and staging

Upon admission, all patients were studied with colonoscopy, abdominal ultrasonography and computed tomography (CT) to gain a correct preoperative staging. All comorbidity was noticed and patients underwent clinical and instrumental examinations. Cardiac diseases were assessed as electrocardiographic or echocardiographic abnormalities, or pathology for which the patient was under specific treatment; vascular pathology as cases of hypertension treated with specific drugs; cerebrovascular pathology; pulmonary diseases as abnormal spirometry, or pathology for which the patient was taking medication. Surgical risk was evaluated preoperatively with ASA score by a senior anesthesiologist. Antibiotic and thromboembolic prophylaxis was performed in all patients. The presence of residual tumor (R category) and tumor stage (TNM) were defined on the basis of the criteria established by the Union International Contre Le Cancer (UICC).

Surgical approach and techniques

The main goal of surgery was the complete removal of the tumour (R0 resection), although palliative resection was performed to treat tumor-related complications. Right and left hemicolectomy, low or very low anterior resection, or transverse colon resection were carried out as standard techniques for CRC, with vessel ligation and respecting oncological criteria. In the event of multiple and synchronous localization, the extent of resection was chosen case by case. Hartmann resection was performed rarely. Definitive loop colostomy or ileostomy was reserved for advanced tumors or patients with very bad performance status in the event of severe bowel obstruction. Temporary covering ileostomy at primary surgery was planned mainly for very low anterior resection for rectal cancer.

Follow-up and statistical analysis

All clinical and surgical data were collected and stored in a PC database. The data concerning follow-up were collected during outpatient clinical examination and by contacting the family physician. The collected data included demographic and clinical characteristics, co-morbidity (cardiovascular, pulmonary and digestive diseases, diabetes mellitus and other tumors), site of neoplasm (colon or rectum), type of surgery (elective or emergency), presence of residual tumour (R0 or R1–2 resection), histological features, tumour stage (TNM) and Dukes' classification,

as well as postoperative morbidity and mortality. A particular effort was made to analyze comorbidity, postoperative complications and survival rates, to identify specific features of the two groups under study. Cardiovascular diseases included heart disease such as myocardial ischemia or valvular disease, both with hypertension and cerebrovascular disorders; and aortic as well as peripheral arterial disorders were also included. Digestive comorbidity included major gastrointestinal, hepatic or biliary-pancreatic diseases such as inflammatory bowel disease, pancreatitis, hepatic cirrhosis and portal hypertension. We also focused on patients who were affected by tumors other than CRC, including them in the "other tumor" comorbidity group. In assessing postoperative complications and mortality, events that occurred during hospitalization or within 30 d after operation were included in the analysis. Diseases such as pulmonary embolism, myocardial ischemia or acute renal failure, and surgical complications, such as anastomotic leakage or abdominal infection, were considered separately. Statistical differences in clinicopathological characteristics and comorbidity between the groups were assessed by the χ^2 test for categorical variables and Student's *t* test for continuous variables. Survival curves were calculated according to the Kaplan-Meier model. Survival curves were calculated for the two groups with regard to overall and disease-specific survival; operative mortality was calculated in the analysis. The log-rank test was used to assess the difference between the two groups. $P < 0.05$ was considered significant.

RESULTS

Clinicopathological findings

Clinicopathological features and presence of comorbidity in the two groups are reported in Table 1. Among the 403 patients, we observed 106 tumors that arose from the rectum, 109 from the right colon, 20 from the transverse colon, and 160 from the descending or sigmoid colon. Multiple tumors were observed in eight cases. Rectal tumors prevailed in group A (31.6% *vs* 19.7%, $P = 0.027$); otherwise, topographic distribution of colon cancer was rather homogeneous between the two groups. Elderly patients underwent emergency operation more frequently compared to younger ones, although the difference was not statistically significant (14% *vs* 9.3%, $P = 0.094$). A potentially curative (R0) resection was achieved with a rate of about 77% in both groups ($P = 0.512$). With respect to the Dukes' and TNM classifications, no significant differences were noted between groups A and B. As regards comorbidity, our findings suggest a significant difference between group A and B with an overall rate of 46.2% and 69.1%, respectively ($P < 0.001$). By analyzing different comorbidity in each group, we found that patients aged ≥ 70 years had a 51.1% rate of cardiovascular diseases compared to 30.7% in the younger ones ($P < 0.001$). Weak differences were noticed between group A and B with respect to pulmonary diseases ($P = 0.048$) and other tumors ($P = 0.050$). Other comorbidity did not show any significant features in either of the populations studied.

Table 1 Clinical and pathological data for group A (< 70 years) and B (≥ 70 years) *n* (%)

	Group A (<i>n</i> = 225)	Group B (<i>n</i> = 178)	<i>P</i>
Sex			
Males	126 (56)	103 (57.9)	0.392
Females	99 (44)	75 (42.1)	
Localization ¹			
Colon	152 (67.6)	141 (79.2)	0.027
Rectum	71 (31.6)	35 (19.7)	
Type of surgery			
Elective	204 (90.7)	153 (86)	0.094
Emergency	21 (9.3)	25 (14)	
Residual tumor			
R0	174 (77.3)	137 (77)	0.512
R+	51 (22.7)	41 (23)	
Comorbidity			
Overall	104 (46.2)	123 (69.1)	0.0001
Cardiovascular diseases			
Absent	156 (69.3)	87 (48.9)	0.0001
Present	69 (30.7)	91 (51.1)	
Pulmonary diseases			
Absent	217 (96.4)	164 (92.1)	0.048
Present	8 (3.6)	14 (7.9)	
Diabetes mellitus			
Absent	211 (93.8)	160 (89.9)	0.106
Present	14 (6.2)	18 (10.1)	
Gastrointestinal diseases			
Absent	198 (88)	158 (88.8)	0.470
Present	27 (12)	20 (11.2)	
Other tumors			
Absent	216 (96)	163 (91.6)	0.050
Present	9 (4)	15 (8.4)	
Dukes' stage			
A	14 (6.2)	8 (4.5)	0.623
B	96 (42.6)	89 (50)	
C	64 (28.4)	41 (23)	
D	51 (22.7)	40 (22.5)	
T stage			
T1	18 (8)	10 (5.6)	0.485
T2	36 (16)	35 (19.7)	
T3	148 (65.8)	110 (61.8)	
T4	23 (10.2)	23 (12.9)	
N stage			
N0	122 (54.2)	110 (61.8)	0.270
N1	64 (28.4)	45 (25.3)	
N2	39 (17.3)	23 (12.9)	
Metastases			
No	174 (77.3)	138 (77.5)	0.530
Yes	51 (22.7)	40 (22.5)	

¹Synchronous localizations of colon and rectum are represented in two cases for each group (0.9% vs 1.1%).

Short-term postoperative results

The distribution of surgical procedures is reported in Table 2. Hartmann resection and palliative stoma were performed rarely, and mostly they were carried out in elderly patients. Concerning the postoperative period, overall morbidity was 16.9% and 20.8% in group A and B, respectively ($P = 0.367$). No significant difference was observed as regards surgical complications, whereas medical adverse events were twofold greater in group B compared to group A (9% vs 4.8%, $P = 0.122$). Among cardiovascular complications, acute heart failure or pulmonary edema was the most common postoperative morbidity. Among surgical complications, the percentage

Table 2 Surgical procedures and postoperative results *n* (%)

	Group A (<i>n</i> = 225)	Group B (<i>n</i> = 178)	<i>P</i>
Postoperative mortality	-	8 (4.5)	0.001
Postoperative complications	38 (16.9)	37 (20.8)	0.367
Surgical complications	27 (12)	21 (11.8)	1
Medical complications	11 (4.9)	16 (9)	0.112
Operation			
Right hemicolectomy	53 (23.6)	61 (34.3)	
Left hemicolectomy	73 (32.4)	50 (28.1)	
Transverse colon resection	5 (2.2)	9 (5.1)	
Abdominoperineal resection	9 (4)	8 (4.5)	
Lower anterior resection	78 (34.7)	43 (24.2)	
Hartmann resection	1 (0.4)	4 (2.2)	
Stoma	2 (0.9)	2 (1.1)	
Miscellaneous	4 (1.8)	1 (0.6)	
Anastomotic leakage rate	10 (4.4)	4 (2.3)	0.282

with anastomosis leakage was 3.5%, with a higher number of cases in group A (4.4% vs 2.3%, $P = 0.282$). Overall postoperative mortality was 2% and it was limited to patients aged ≥ 70 years (4.5%, $P = 0.001$) (Table 2).

Preexisting comorbidity and short-term results

Table 3 shows the correlation between clinicopathological features, preexisting comorbidity and the occurrence of postoperative complications. The overall comorbidity rate was significantly higher in patients who developed postoperative complications in groups A and B. In group A, male patients experienced complications more frequently than females ($P = 0.049$). In group B, preexisting cardiovascular diseases were significantly associated with postoperative complications ($P = 0.003$). Other features did not influence significantly the postoperative course.

Survival analysis

The 5-year survival rate for all 403 patients was 62.9%, whereas it was 76.4% for the R0-resected patients. Considering all causes of death, the overall 5-year survival rate was significantly better for group A (75.2% vs 55%, $P = 0.006$) (Figure 1). Conversely, considering disease-specific survival (postoperative and tumor-related deaths only), no difference was observed between groups A and B (76.3% vs 76.9%, $P = 0.674$) (Figure 2).

DISCUSSION

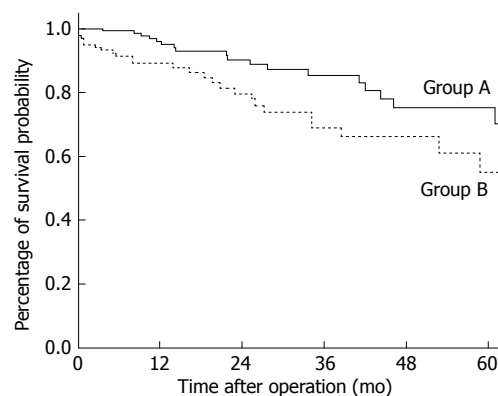
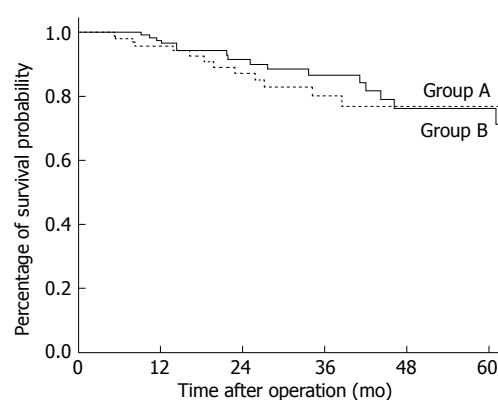
CRC in the elderly

As for other tumors, the development of CRC is associated with increasing age. The reason for cancer development in the elderly can be explained by a longer duration of exposure to carcinogens, a lower ability to repair damaged DNA, and oncogene amplification or tumor suppressor gene malfunction. Furthermore, the progressive loss of immune surveillance can be considered to occur with aging^[8,16]. Despite progress in surgical and perioperative care, a lot of physicians evaluate elderly patients by their chronological rather than biological age^[17]. This attitude may explain why treatment is frequently conditioned in elderly people with malignancies. As a consequence, their therapeutic

Table 3 Correlation between clinicopathological features and preexisting comorbidity with postoperative complications in group A (< 70 years) and B (\geq 70 years) *n* (%)

	Postoperative morbidity			
	Group A (<i>n</i> = 38)	<i>P</i>	Group B (<i>n</i> = 37)	<i>P</i>
Sex				
Male	27 (71.1)	0.049	23 (62.2)	0.58
Female	11 (28.9)		14 (37.8)	
Localization				
Colon	23 (60.5)	0.344	26 (70.3)	0.171
Rectum	15 (39.5)		11 (29.7)	
Type of surgery				
Elective	32 (84.2)	0.136	30 (81.1)	0.424
Emergency	6 (15.8)		7 (18.9)	
Residual tumor				
R0	27 (71.1)	0.297	29 (78.4)	0.505
R+	11 (28.9)		8 (21.6)	
Comorbidity				
Overall				
Yes	25 (65.8)	0.012	32 (86.5)	0.01
No	13 (34.2)		5 (13.5)	
Cardiovascular diseases				
Absent	22 (57.9)	0.122	10 (27)	0.003
Present	16 (42.1)		27 (73)	
Pulmonary diseases				
Absent	36 (94.7)	0.625	32 (86.5)	0.172
Present	2 (5.3)		5 (13.5)	
Diabetes mellitus				
Absent	34 (89.5)	0.264	34 (91.9)	0.769
Present	4 (10.5)		3 (8.1)	
Gastrointestinal diseases				
Absent	30 (78.9)	0.095	32 (86.5)	0.571
Present	8 (21.1)		5 (13.5)	
Other tumors				
Absent	36 (94.7)	0.65	32 (86.5)	0.314
Present	2 (5.3)		5 (13.5)	
T stage				
T1-T2	5 (13.2)	0.098	12 (32.4)	0.29
T3-T4	33 (86.8)		25 (67.6)	
N stage				
N0	15 (39.5)	0.051	23 (62.2)	0.559
N+	23 (60.5)		14 (37.8)	
Dukes' stage				
A	1 (2.6)	0.385	3 (8.1)	0.669
B	13 (34.2)		17 (45.9)	
C	13 (34.2)		9 (24.3)	
D	11 (28.9)		8 (21.6)	
Metastases				
No	27 (71.1)	0.297	29 (78.4)	0.542
Yes	11 (28.9)		8 (21.6)	

management remains controversial. As a result of their age, elderly people usually suffer from other chronic illnesses in addition to colorectal malignancy. Nonetheless, surgical resection remains the treatment of choice, probably because surgery still represents the mainstay of therapy for CRC, and the most used option to treat bowel obstruction. In a recent study by Lemmens *et al*^[18], it has been demonstrated that age > 70 years, a tumor located in the rectum, emergency surgery, and the presence of concomitant chronic obstructive pulmonary disease or deep vein thrombosis increase the risk of developing a surgical complication. On the contrary, CRC patients without comorbidity developed surgical complications in < 30% of the cases.

**Figure 1** Kaplan-Meier estimates of survival probability for R0 population in group A (< 70 yr; 174 pts) and B (\geq 70 yr; 137 pts). Postoperative, tumor-related and -unrelated deaths were included (Log-rank test, *P* = 0.006).**Figure 2** Kaplan-Meier estimates of disease-specific survival probability for R0 population in group A (< 70 yr; 174 pts) and B (\geq 70 yr; 137 pts). Postoperative and tumor-related deaths were included (Log-rank test, *P* = 0.674).

Postoperative morbidity

With reference to our results, we had a comparable postoperative morbidity rate^[19], with no statistically significant difference between the two groups. Considering medical complications, elderly patients had a twofold greater, even though not significant, rate of adverse events such as pulmonary embolism and myocardial ischemia. This may be due to a higher prevalence of cardiovascular diseases at the time of cancer diagnosis. Our previous study supports these data that show that cardiac complications are the most frequent in octogenarians affected by gastrointestinal carcinoma^[20,21]. Based upon our findings, cardiovascular comorbidity has a significant influence on the development of postoperative complications in elderly as well as younger patients. As regards postoperative complications, we observed a low rate of complications with no difference between the two groups. Our data seem to confirm the possibility of achieving a very low percentage of adverse events in aged patients, with curative resection and overall anastomotic leakage rates equally successful in both groups.

Comorbidity and postoperative complications

Current literature supports the notion that a higher mortality rate in older patients can be attributed mainly to preexisting comorbid conditions^[10,22], such as congestive

heart failure, diabetes mellitus and chronic obstructive pulmonary disease^[23]. It also emphasizes the role of interactions between disease conditions and CRC, and suggests that multiple comorbidity has a substantial effect on long-term survival. The number of comorbid conditions increases with age and the most frequent diseases are hypertension, other cardiovascular diseases and previous malignancy^[1,12]. In agreement with other experiences, male patients have a higher prevalence of postoperative complications compared to females^[24], and an explanation may be found in the lower number of women suffering from cardiovascular diseases, especially at younger ages. Our data confirmed that elderly patients, in spite of an equal percentage of postoperative complications, have a higher mortality rate compared to younger patients^[7,10,25,26]. The relationship between preoperative comorbid conditions and postoperative mortality has been demonstrated by previous studies^[10,23,27-30]. Moreover, we assessed that in most of the eight patients who died, there was more than one comorbid condition. These results suggest that postoperative complications are tolerated poorly by elderly patients, particularly those suffering from comorbidity.

Overall and tumor-related survival

In the elderly population with CRC, the relationship between age and long-term outcome after surgery remains not yet completely defined, and the results on survival are still a matter of debate, with alternative conclusions^[3,7]. Regarding overall survival, it has been demonstrated that it decreases with aging^[1]. Nonetheless, disease stage influences specific tumor survival independently of age. It has been reported that the decrease in survival is more evident in very old patients, particularly those aged > 85 years. In this regard, our findings clarify that elderly people have a significantly worse overall survival rate compared to younger ones, but, after censoring cancer-unrelated deaths, survival rates become comparable. Thus, strictly considering tumor-related mortality, no difference was observed between the two groups. Other authors have supported our results^[2] and have emphasized the relationship between early stage of the disease and a similar prognosis in elderly compared to younger patients. In spite of an increase in postoperative mortality and a shorter overall long-term survival for patients aged \geq 70 years, it should be considered that, even among elderly patients, a significant number of patients is alive 5 years after CRC resection.

In conclusion, in agreement with previous studies, our findings suggest that a relevant positive outcome after a potentially curative resection should encourage surgical treatment of elderly patients with CRC. Comorbidity represents a risk factor for developing postoperative complications in younger and older patients. A higher risk of postoperative mortality seems to be a prerogative of elderly patients affected by other comorbid conditions, especially cardiovascular diseases. As a consequence, surgeons should be more cautious when confronted with elderly patients suffering from severe comorbidity. Even if treatment decisions in elderly patients with CRC should be

made on the basis of careful evaluation of cardiovascular and pulmonary parameters, surgical tumor resection clearly is encouraged by high rates of potentially curative resection and satisfactory long-term survival results.

COMMENTS

Background

Colorectal cancer (CRC) generally is considered to be a disease of the elderly. Several studies have reported that elderly patients with CRC can be treated by standard surgical resection, although some debate still exists on this topic.

Research frontiers

The correlation between preexisting comorbidity, clinicopathological features, and short- and long-term outcomes was studied in elderly patients undergoing surgery for CRC.

Innovations and breakthroughs

A particular effort has been made to analyze preexisting comorbidity, postoperative complications and long-term results, to identify features specific for elderly patients compared to younger ones.

Applications

In spite of an acceptable increase in postoperative mortality and a shorter overall long-term survival, surgical resection provides encouraging results for patients aged \geq 70 years.

Peer review

The authors investigated the relationship between preexisting diseases and other clinicopathological features, perioperative surgical outcome, and survival in elderly patients with CRC treated by surgery. The conclusions are definite, and the contents are well-organized and well-written. The results give us some new ideas about the elderly population undergoing surgery for CRC.

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