Original Article

Risks Factors for Postoperative Mortality after Colorectal Cancer Resection

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Key Words
Colorectal cancer;
Postoperative mortality;
Complication

Purpose. Colorectal cancer surgery is associated with a 1.3%-8.5% mortality rate. The variation in these outcomes may be attributed to the quality of care. This study aimed to identify independent risk factors for postoperative mortality.
Methods. Patients that underwent resection for colorectal cancer in a single medical center from January 1993 to December 2011 were identified from a prospectively maintained database. Data including clinicopathological features, operation methods, and in-hospital complications were collected. Postoperative mortality was defined as death within 90 days after surgery. The risks factors were analyzed by logistic regression analysis.
Results. There were 5609 patients included in this study. The mean age of the patients was 62.6 years, and 3591 (62.0%) were male. Among these patients, 134 patients died within 90 days. The postoperative mortality rate was 2.4%, and the in-hospital complication rate was 21.5%. Independent risk factors for postoperative mortality were age ≥ 65 years, postoperative complications (especially cardiopulmonary complications), elevated carbohydrate antigen 19-9, and lymphoma.
Conclusions. Recognition of these risk factors could help to improve the care of patients with colorectal cancer preparing for surgery.
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Colorectal cancer is the most common cancer in Taiwan with at least 15140 new cases diagnosed in 2013 and the third most common cause of cancer-related mortality according to statistics from the Taiwan cancer registry. The incidence rate is 64.7 per 100000 people. The incidence rate of colorectal cancer increases annually in Taiwan, and the average annual percentage change was 4.3% for colon cancer and 1.4% for rectal cancer between 2002 and 2012.[1]

Even with great improvements in chemotherapy and targeted therapy in colorectal cancer, surgery is still viewed as the primary treatment option. Nonetheless, colorectal cancer resection is associated with a 1.3%-8.5% 30-day postoperative mortality rate, mainly identified in patients from Europe.[2-5] The great variation in survival rates may reflect the impact of quality of care.

The most frequently cited statistics almost always use 30 days as the benchmark for postoperative death.[2,4-6] Due to increasing knowledge in intensive

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care practice and the establishment of early goal-directed therapy in recent years, the surgical risk following surgery most likely extends beyond 30 days. Mamidanna et al. revealed that patients who underwent colorectal resection have a higher mortality rate at 90 days following surgery; their study in 2015 demonstrated that mortality risk is underestimated when only 30-day statistics are reported.[7]

This study describes short-term outcomes following surgical resection for colorectal cancer. We reviewed data including clinical characteristics, pathological tumor features and postoperative complications following colorectal cancer surgery in Taipei Veterans General Hospital. Our aim was to determine the risk factors for 90-day postoperative mortality in patients that underwent colorectal cancer resection to improve the quality of perioperative care.

Materials and Methods

This study included all colorectal cancer (CRC) patients that underwent resection from January 1993 to December 2011 in Taipei Veterans General Hospital, and these data were reviewed retrospectively from a prospectively constructed database. Patients who received transanal resection only and those lost to follow-up within 90 days after surgery were excluded. Clinical characteristics, preoperative serum tumor markers (carcinoembryonic antigen [CEA] and carbohydrate antigen 19-9 [CA 19-9]), American society of anesthesiologists (ASA) score, cancer site, histology and American joint committee on cancer (AJCC) stage according to pathology findings were derived from the database. As for classification of underlying diseases, cardiopulmonary history included congestive heart failure, previous myocardial infarction, coronary artery disease, chronic obstructive pulmonary disease (COPD), and hypertension; brain disease included stroke and dementia. Surgery was categorized into right hemicolectomy, transverse colectomy, left hemicolectomy, anterior resection, low anterior resection, Hartmann's procedure and total/subtotal colectomy. Cancers located from the cecum up to the transverse colon were classified into the right-sided colon lesion group, and the left-sided colon cancer group included lesions of the splenic flexure, descending colon, sigmoid colon and rectosigmoid junction. Postoperative complications that occurred within the 90-day period after operation were included, and the types of complication are listed in Table 1. Cardiopulmonary complications included acute decompensated heart failure, arrhythmia, myocardial infarction, pneumonia, pneumothorax and pulmonary embolism. Death within 90 days after surgery were defined as postoperative mortality, and complications that occurred within this 90-day period were viewed as postoperative complications.

Statistical analyses were carried out using SPSS Version 20.0. Comparison of categorical variables was performed using the chi-square test. Continuous variables were compared using the Mann-Whitney U test. Multivariate Cox proportional models were used to identify independent risk factors for postoperative mortality. Variables with $p < 0.05$ by univariate analyses were entered into the multivariate model. A two-sided $p < 0.05$ was considered statistically significant.

Table 1. Type of complication

	n	%
Wound infection	489	8.72%
Anastomosis leakage	205	3.65%
Ileus	244	4.35%
Urinary tract infection	115	2.05%
Pneumonia	86	1.53%
Urine retention	65	1.16%
Wound dehiscence	61	1.09%
Chyle leakage	57	1.02%
Intra-abdominal abscess	55	0.98%
Acute decompensated heart failure	28	0.50%
Ureter injury	33	0.59%
Anastomosis bleeding	20	0.36%
Stroke	19	0.34%
Acute myocardial infarction	19	0.34%
Atelectasis	19	0.34%
Acute kidney injury	17	0.30%
Arrhythmia	16	0.29%
Enterocutaneous fistula	15	0.27%
Deep venous thrombosis	13	0.23%
Pneumothorax	7	0.12%
Rectovaginal fistula	6	0.11%
Pulmonary embolism	4	0.07%
Postoperative hepatitis	15	0.27%

Results

Between January 1993 and December 2011, 5831 patients diagnosed with CRC underwent surgical resection at our institute. There were 194 patients who were lost to follow-up within 90 days. Therefore, 5609 patients were included in the study. The mean age of the patients was 62.6 years and 3591 (62.0%) were male. Among them, 134 patients died within 90 days after surgical resection and the perioperative mortality rate was 2.4%.

The univariate and multivariate analyses of patient demographics data for postoperative mortality are listed in Table 2 and Table 3. Notably, age ≥ 65, cardiopulmonary complications, and elevated level of CA-199 were significantly associated with postoperative death. However, there were no significant differences between the two groups in terms of sex, tumor size, tumor location, emergency surgery, or other surgery types. Underlying cardiopulmonary disease and ASA score adversely affected the postoperative outcome in univariate analysis, but the effects were not demonstrated in the multivariate study.

Table 4 summarizes univariate and multivariate analyses based on histopathological data for postoperative mortality. Though AJCC stage, poor differentiation, and different histology patterns were identified as risk factors in the univariate analysis, lymphoma was the only significant factor associated with poor perioperative outcome in multivariate analysis.

Postoperative complications were observed in 1208 patients (21.5%) (Table 1). Wound infection was the most common surgical complication (n = 489, 8.8%), followed by postoperative ileus (n = 244, 4.4%). Anastomotic leakage occurred in 204 patients (3.7%). Other complications were as follows: urinary tract infection (n = 115, 2.1%); pneumonia (n = 78, 1.40%); chyle leakage (n = 57, 1.00%); acute decompensated heart failure (n = 28, 0.50%). Cardiopulmonary complication (including heart failure, arrhythmia, acute myocardial infarction, pneumonia and pulmonary embolism) was the only significant risk factor associated with postoperative mortality.

The underlying causes of postoperative mortality

Table 2. Patient demographics and uni- and multivariate analyses of 90-day postoperative mortality

	Patients that survived (n = 5475)	Patients that died within 90 days (n = 134)	Univariate analysis *p* value	Multivariate analysis OR (95% CI)	Multivariate analysis *p* value
Age			0.001		
Median (range)	65 (13-108)	73 (22-92)			
Age < 65	2782 (50.8%)	45 (33.6%)		1	
Age ≥ 65	2693 (49.2%)	89 (66.4%)		2.58 (1.38-4.82)	0.003
Sex			0.85		
Male	3499 (63.9%)	92 (68.7%)			
Female	1976 (36.1%)	42 (31.3%)			
Family history			0.35		
No	4367 (79.8%)	116 (86.6%)		1	
Yes	1108 (20.2%)	18 (13.4%)		0.81 (0.37-1.78)	0.592
ASA			0.01		
ASA I, II	4018 (73.4%)	74 (55.2%)		1	
ASA III or higher	1457 (26.6%)	60 (44.8%)		1.21 (0.66-2.23)	0.540
Underlying disease					
Liver cirrhosis	157 (2.9%)	5 (3.7%)	0.40		
Cardiopulmonary history	2520 (46.0%)	81 (60.4%)	0.001	1.23 (0.71-2.12)	0.468
Brain disease	273 (5.0%)	9 (6.7%)	0.23		
Complication	1143 (20.9%)	75 (56.0%)	0.001	3.43 (2.00-5.90)	0.001
Anastomosis leakage	191 (3.5%)	13 (9.7%)	0.001	1.10 (0.57-2.13)	0.768
Cardiopulmonary complication	91 (1.7%)	39 (29.1%)	0.001	23.30 (10.57-51.38)	0.001

ASA: American Society of Anesthesiologists; CI: confidence interval; OR: odds ratio.

Table 3. Univariate and multivariate analyses of perioperative data on 90-day postoperative mortality

	Patients that survived (n = 5475)	Patients that died in 90 days (n = 134)	Univariate analysis *p* value	Multivariate analysis OR (95% CI)	Multivariate analysis *p* value
Preoperative data					
CEA					
Median (range)	3.7 (0.01-8790)	12.7 (0.58-13382)			
CEA < 5	3244 (62.0%)	41 (33.9%)		1	
CEA ≥ 5	1990 (38.0%)	80 (66.1%)	0.001	1.88 (0.96-3.67)	0.065
CA 19-9					
Median (range)	2.5 (0.01-58085)	25.6 (1.37-13353)			
CA 19-9 < 37	3883 (93.3%)	39 (54.2%)		1	
CA 19-9 ≥ 37	277 (6.7%)	33 (45.8%)	0.001	3.62 (1.78-7.38)	0.001
Preoperative chemotherapy	449 (8.2%)	10 (7.5%)	0.53		
Preoperative radiotherapy	369 (6.7%)	5 (3.7%)	0.93		
Simultaneous fecal diversion	1186 (21.7%)	38 (28.4%)	0.02	1.10 (0.49-2.47)	0.83
Emergency	238 (4.3%)	26 (19.4%)	< 0.001	1.07 (0.36-3.17)	0.897
Obstruction	171 (3.1%)	15 (11.2%)	< 0.001	1.46 (0.50-4.29)	0.487
Perforation	50 (0.9%)	8 (6.0%)	< 0.001	0.31 (0.02-4.08)	0.375
Laparoscopy	908 (16.6%)	4 (3.0%)	0.001	0.45 (0.14-1.49)	0.189
Surgery type					
Right hemicolectomy	1403 (25.6%)	42 (31.3%)	0.004	1.67 (0.85-3.27)	0.138
Left hemicolectomy	416 (7.6%)	4 (3.0%)	0.32	1.21 (0.40-3.67)	0.740
AR/LAR	3177 (58.0%)	61 (45.5%)		1	
APR	274 (5.0%)	4 (3.0%)	0.71	0.76 (0.17-3.31)	0.710
Total/subtotal colectomy	128 (2.3%)	2 (1.5%)	0.41	1.11 (0.22-5.54)	0.904
Hartmann procedure	53 (1.0%)	8 (6.0%)	0.001	3.47 (0.77-15.61)	0.105
Concomitant resection	813 (14.8%)	23 (17.2%)	0.08		

APR: abdominoperineal resection; AR: anterior resection; CA 19-9: carbohydrate antigen 19-9; CEA: carcinoembryonic antigen; CI: confidence interval; LAR: low anterior resection; OR: odds ratio.

Table 4. Uni- and multivariate analyses of histopathological data on 90-day postoperative mortality

	Patients that survived (n = 5475)	Patients that died in 90 days (n = 134)	Univariate analysis *p* value	Multivariate analysis OR (95% CI)	Multivariate analysis *p* value
Location					
Right	1487 (27.2%)	53 (39.6%)		1	
Left	2281 (41.7%)	48 (35.8%)	0.15	0.77 (0.20-2.98)	0.704
Rectum	1707 (31.1%)	33 (24.6%)	0.12	0.68 (0.15-3.03)	0.617
Tumor size					
Tumor < 5 cm	3588 (65.6%)	90 (71.4%)			
Tumor ≥ 5 cm	1878 (34.4%)	36 (28.6%)	0.21		
Histology					
Adenocarcinoma	5016 (91.6%)	122 (91.0%)		1	
Mucinous tumor	235 (4.3%)	4 (3.0%)	0.64	0.39 (0.09-1.76)	0.223
Signet ring cell carcinoma	59 (1.1%)	4 (3.0%)	0.03	1.43 (0.17-11.96)	0.740
Lymphoma	8 (0.1%)	2 (1.5%)	0.002	88.72 (3.11-2527.83)	0.009
Others	133 (2.4%)	2 (1.5%)	0.63	1.02 (0.11-9.34)	0.983
Differentiation					
Mild	330 (6.0%)	4 (3.0%)		1	
Moderate	4552 (83.1%)	96 (71.6%)	0.30	0.40 (0.13-1.24)	0.113
Poorly	312 (5.7%)	18 (13.4%)	0.007	0.62 (0.16-2.47)	0.501
Undifferentiated	11 (2.0%)	1 (0.7%)	0.082		0.999
No data	270 (4.9%)	15 (11.2%)	0.46	0.30 (0.05-1.82)	0.192
Stage					
Tis	309 (5.6%)	6 (4.5%)		1	
1	943 (17.2%)	11 (8.2%)	0.81	1.50 (0.30-7.63)	0.624
2	1724 (31.5%)	20 (14.9%)	0.87	0.75 (0.15-3.77)	0.724
3	1549 (28.3%)	24 (17.9%)	0.47	1.02 (0.21-5.00)	0.984
4	948 (17.3%)	73 (54.5%)	0.001	2.56 (0.58-11.4)	0.217

CI: confidence interval; OR: odds ratio.

were studied. Sixty-two patients died within 30 days, of whom 37 (59.7%) died from surgical complications and 23 (37.1%) died of diseases. In the 90-day mortality group, 53 (39.6%) died from surgical complications and 74 (55.2%) died of diseases.

Discussion

This retrospective single center study is the first to evaluate postoperative mortality in patients that underwent colorectal cancer surgery in Asia. This prospectively constructed database provides a comprehensive perspective allowing review of the effects of perioperative events on postoperative outcomes. The overall 30-day and 90-day postoperative mortality rates in our study were 1.1% and 2.4%, respectively, which are comparable with previous studies showing that 30-day postoperative mortality ranged from 1.3% to 8.5%.[2,4,5] Our data demonstrated that 90-day postoperative mortality is associated with age ≥ 65, postoperative complications (especially cardiopulmonary complications), elevated CA 19-9 and lymphoma.

The postoperative complication rate was 21.7%, which is lower than the results reported in previous studies[2,3,8] and reflects the quality of care provided through our institute. The postoperative complications are of particular importance because they revealed significant influence on postoperative mortality not only in our study but also in others.[5,9,10] Among these complications, cardiopulmonary conditions including acute decompensated heart failure, arrhythmia, myocardial infarction, pneumonia and pulmonary embolism, were identified as significant risk factors for multivariate analysis. Similar results were observed in several other quality improvement studies. The American college of surgeons National Surgical Quality Improvement Program (ACS NSQIP) study determined that COPD and dyspnea before operation were significant risk factors for both mortality and morbidity.[11] Moreover, cardiopulmonary complications were the most common type of failure-to-rescue complication in patients after colorectal cancer resection in a national quality improvement project from the Netherlands.[12] These results remind physicians to pay more attention to the postoperative cardiopulmonary status of patients after colectomies in all clinical practices.

Old age is an independent adverse factor for poor short-term outcomes after colon resection. Old age was identified as a risk factor in previous studies.[2,5,10] Grosso et al. performed a case control study to assess the odds of having a complication and investigated the different types of complication between patients older than 65-years-old and younger patients. Though intraoperative complications did not differ between younger and older patients, the elderly had a higher incidence of postoperative and late complications. Importantly, older patients tend to suffer more from systemic complications such as cardiovascular complications compared with younger patients.[13] Correlating these results with our study, cardiopulmonary complications also have an adverse effect on postoperative mortality, and the poorer postoperative outcomes in elderly patients may be attributed to the higher incidence of postoperative complications. This reinforces the significance of careful preoperative cardiopulmonary evaluation and postoperative cardiopulmonary care for older patients undergoing colorectal resection.

Elevated CA 19-9 also has an adverse impact on postoperative outcome. However, after multivariate logistic regression analyses, elevated CA 19-9 was associated with poor differentiation and late AJCC stage, as reported in other studies.[14-16] Zhong et al. reported that serum levels of CEA, CA19-9, cancer antigen 125 (CA125), cytokeratin 19 fragment CYFRA21-1, and cancer antigen 72-4 (CA72-4) were not associated with age, sex, pathological type or location of cancer (all $p > 0.05$), but were associated with poor tumor differentiation, higher tumor invasion, greater degree of abdominal lymph node metastasis, and higher TNM and Duke stage tumors.[14] Additionally, elevated CA 19-9 may indicate poor tumor differentiation and advanced tumor stage, which might translate into difficulties in surgery and affect the postoperative outcome.

Lymphoma was a risk factor for poor short-term outcome in our study. Primary colorectal lymphoma is

a rare tumor and comprises only 0.2-0.6% of all colorectal malignancies.[17] The incidence rate in our study was 0.18% (10/5,609), and two patients died within 90 days. One patient died because of multiple liver metastases and severe liver cirrhosis, and the other one received emergency operation due to perforation and eventually died of stroke and empyema. In a previously published study, the occurrence of lymphoma requiring emergency operation was associated with high mortality (53.3%) due to advanced stage and the high risk of postoperative complications.[18] However, the small number of cases may have interfered with statistics. Nevertheless, these results suggest that more attention should be paid when taking care of patients with colon lymphoma.

We also compared the cause of death in the 90-day timeframe with the 30-day timeframe; the percentage of deaths related to colorectal cancer increased at 90 days (37.1% vs. 55.2%), while the percentage of deaths related to surgical complications decreased (59.7% vs. 39.6%). This observation corresponds to the previous study by Mamidanna et al. They analyzed timing and causes of mortality following colorectal cancer resection, and the deaths attributed to colorectal cancer increased over time.[7] Nonetheless, there were still a significant number of patients that died from surgical related complications, which again reiterates the need for subtle post-operative care.

There was a limitation to our study. Because this was a retrospective study, some perioperative data that might influence surgical outcomes, e.g. blood loss and operation time, were not included in our database.

Conclusions

In conclusion, colorectal cancer resection was associated with a 2.4% 90-day mortality rate in our study. Risk factors, including old age, postoperative complications (especially cardiopulmonary complication), elevated CA 19-9, and lymphoma, significantly increased postoperative 90-day mortality in patients following resection for colorectal cancer. Awareness of these risk factors may help to optimize the treatment plan for patients undergoing colorectal cancer resection.

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原　著

大腸直腸癌術後死亡之危險因子探討

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目的　在過去研究中，病患接受腸切除術後的死亡率約 1.3% 到 8.5%。這些術後存活率的差異可能與病患術前評估及術後照護的品質有關。本篇研究主要目的是要探討可能影響大腸直腸癌病患接受腸切除術後死亡的可能因子。

方法　研究主要是從前瞻性建立之資料庫回溯統計從 1993 年 1 月至 2011 年 12 月期間於單一醫學中心因大腸直腸癌接受腸切除手術的病患。研究主要評估癌症的部位、病理分期、病患年齡、性別、共病情況、手術方式、術前輔助治療、及術後併發症等因子。術後死亡率定義為病患在接受術後 90 天內死亡。這些可能危險因子與術後死亡率之相關性是以多元邏輯迴歸分析作統計。

結果　共有 5609 位大腸直腸癌病患接受腸切除手術。病患群的平均年齡為 62.6 歲，而其中有 3591 (62%) 名病患為男性。在其中共有 134 名病患於術後 90 天內死亡。其術後死亡率為 2.4%；而術後併發症發生率為 21.5%。經多變項分析後，可能影響病患接受大腸直腸癌切除手術後死亡的獨立因子包括病患年齡 ≥ 65 歲、術後併發症 (尤其心肺相關併發症)、CA 19-9 > 37 U/ml 和淋巴癌。

結論　在本篇研究中，病患年齡 ≥ 65 歲、術後併發症 (尤其心肺相關併發症)、CA 19-9 > 37 U/ml 和淋巴癌為可能影響病患因大腸直腸癌接受腸切除手術後死亡的危險因子。在安排具有以上這些危險因子之大腸直腸癌症病患接受腸切除手術時應更加注意，以期增進大腸直腸癌腸病患之照護醫療品質。

關鍵詞　大腸直腸癌、術後死亡率、併發症。