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Impact of Postoperative Complications on the Long-Term Outcome of Colorectal Cancer Patients who Underwent Curative Resection

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Abstract

Aim: The study evaluated the impact of postoperative complications on long-term outcomes in patients after curative resection for Colorectal Cancer (CRC).

Methods: Patients undergoing curative resection for CRC from January 1993 to December 2009 were identified from a prospectively maintained database. Postoperative complications were graded through Clavien-Dindo classification, and the patients were divided into minor (grade 1 and grade 2) and major (grade 3 and grade 4) complication groups. Factors potentially affecting disease-free survival (DFS) and overall survival (OS) were examined using univariate and multivariate analyses.

Results: A total of 3 666 patients (2 375 men, 64.8%) were included. Complications developed in 823 patients (22.4%), of which 313 (8.5%) were major and 510 (13.9%) were minor complications. The 5-year OS rates for those with major, minor, and no complications were 69.3%, 79.4%, and 86.1% (P<0.001), respectively, whereas the 5-year DFS rates were 62.9%, 71.1%, and 79.7 % (P<0.001), respectively. Major complications were negative predictors of both OS (stage II: hazard ratio [HR]=2.174, 95% confidence interval [CI]: 1.510-3.129, P<0.001; stage III: HR=2.026, 95% CI: 1.482–2.771, P<0.001) and DFS (stage II: HR=1.499, 95% CI: 1.165-1.928, P=0.002; stage III: HR=1.515, 95% CI: 1.226-1.872, P<0.001) in stage II and III patients.

Conclusion: Postoperative complications adversely affect the long-term outcomes of CRC patients after curative resection. The impact of major complications was particularly strong in stage II and III patients.

Keywords: Colorectal; Postoperative complication; Recurrence; Survival

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Introduction

Colorectal Cancer (CRC) is the most frequently diagnosed cancer and the third leading cause of cancer death in Taiwan. Surgical resection remains the mainstay cure for patients with localized disease; however, postoperative morbidity and mortality are considerable. Postoperative complications are associated with a prolonged hospital stay and a higher reoperation rate, as well as a higher hospitalization cost. The postoperative morbidity of patients who underwent colorectal surgery has been well surveyed in previous studies, and ranges from 27.3% to 40.2%; this is high compared with the operative mortality of these patients [1-3]. Prior research has addressed the negative influences of postoperative complications on long-term outcomes in various cancers, including hepatocellular carcinoma, pancreatic cancer, gastric cancer, lung cancer, and CRC [3-7]. One retrospective study demonstrated that postoperative complications adversely affected not only long-term survival but also the disease recurrence rate in patients who underwent curative resection for CRC; however, the severity of the complications was not classified.3 Another retrospective study explored the relation between postoperative morbidity and the outcomes of CRC patients receiving elective resection; the researchers determined that major complications reduced 5-year survival, but had no significant impact on time to recurrence [8]. A third retrospective study examined 12 075 cases from the Veterans Affairs Surgical Quality Improvement Program and Central Cancer Registry database, and demonstrated that the presence of postoperative complications after CRC resection is associated with decreased long-term survival, independent of patient, disease, or treatment factors.

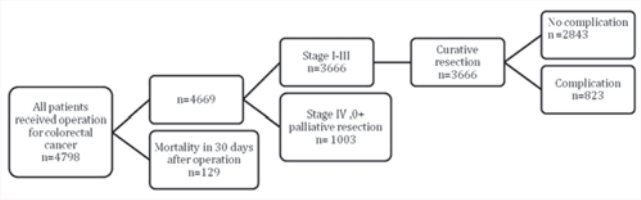

Figure 1: Flowchart of the identification of the study cohort.

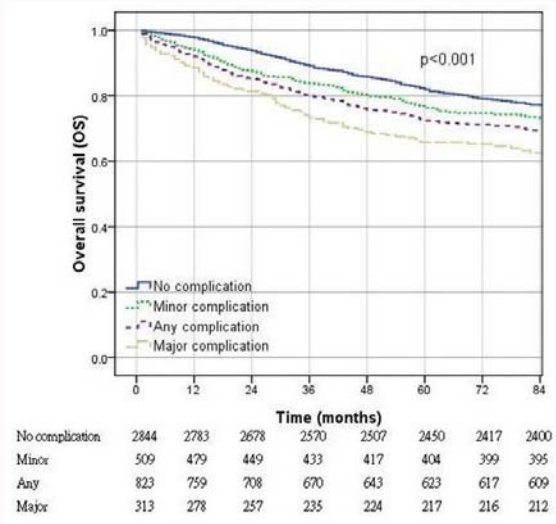

Figure 2: Kaplan-Meier curves comparing overall survival of patients with different complication severities (*P*<0.001, log rank test).

Notably, this study recruited male participants in a proportion higher than 90%, and it lacked the data of disease recurrence outcomes [9]. Therefore, the influence of postoperative complications on long-term outcomes following CRC tumor resection deserves additional clarification. This study aimed to elucidate the effect of postoperative complications on disease recurrence and survival in CRC patients after curative resection in a tertiary referral center.

Material and Methods

Patients who underwent curative resection for CRC from January 1993 to December 2009 at Taipei Veterans General Hospital were reviewed from a prospectively maintained computerized database. Patient characteristics included age, gender, Charlson-Age Comorbidity Index (CACI), types of operation and oncological characteristics comprised of tumor size, lymph node harvest, adjuvant radiotherapy or chemotherapy were collected as baseline variables. The preoperative staging included colonoscopy, serum tumor marker (CEA, CA-199) measurements, chest X-ray or chest Computed Tomography (CT), abdominal CT, and magnetic resonance imaging of the pelvis for patients with rectal cancer. Patients diagnosed with CRC associated with inflammatory bowel diseases or familiar adenomatous polyposis, who were at stage 0 or IV, or who had had palliative resections or local excision without radical resection were excluded. The tumor site was classified as being in the right or left of the colon (either proximal or distal to the splenic flexure) and rectum. The preoperative stage was documented according to the American Joint Committee on Cancer (AJCC Version 6.0) staging system. Complications that occurred within 1 month of the operation were recorded as postoperative complications. If there were more than one complication occurred in the same patient, the complication

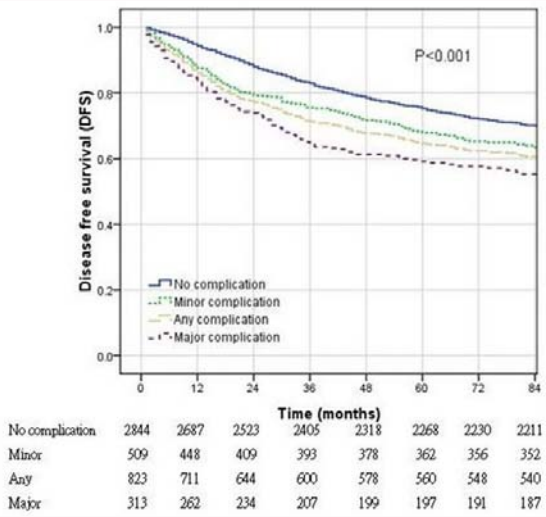

Figure 3: Kaplan-Meier curves comparing disease-free survival of patients with different complication severities (*P*<0.001, log rank test).

that caused the worst severity was shown in Table 2. Complication severity was categorized according to the Clavien-Dindo classification system; the patients were divided into the major complication group, which comprised grade 3 or 4 complications (requiring surgical, radiological, or endoscopic intervention or intensive care) or minor complication group, which comprised grade 1 or 2 complications (requiring conservative or medical treatment only).

In stage III disease cases, postoperative chemotherapy was administrated. For stage II patients with poor prognostic histological features (i.e., poor differentiation, perineural invasion, lymph vascular invasion, <12 harvested lymph nodes) or who presented with tumor perforation, bleeding, or obstruction, 5-fluorouracil-based adjuvant chemotherapy was recommended. In cases of rectal cancer, patients with radiological evidence of T3 or T4 lesions, or lymph node invasion, underwent preoperative chemo radiation therapy and radical resection 6weeks to 8 weeks later routinely since 2000. Before 2000, the patients with locally advanced rectal cancer would have neo adjuvant therapy according to the individual conditions and the opinions from their Attending Physicians in charge.

All patients were followed up at an outpatient department every 3 months for the first 2 years, every 6 months for the third and fourth years, and annually thereafter. Follow-up examinations included a thorough physical examination, serum tumor marker (CEA, CA-199) measurements, a chest X-ray, and abdominal ultrasonography. Abdominal, pelvis, or chest CT was scheduled annually, or performed whenever recurrence was suspected. Operative mortality was defined as death that occurred within 30 days of the primary operation. In the analysis of survival and recurrence, patients who died within 30 days of the operation were excluded.

Primary outcome measures comprised Overall Survival (OS) and disease-free survival (DFS). A patient was considered disease free if no evidence of clinical, endoscopic, or radiological recurrence was noted during follow-up.

Data Analysis

Statistical analyses were carried out using SPSS Version 16.0. Categorical variables were compared using a chi-square test, whereas continuous variables were compared using the Mann-Whitney U

Table 1: Clinicopathological Data of the Patients.

	No complication (n=2844)	Minor complication(n=510)	Major complication (n=313)
Gender			
Male	1789(62.9%)	356(69.8%)	230(73.5%)
Female	1054(37.1%)	154(30.2%)	83(26.5%)
Age(mean ± SD)	67.7 ± 12.9	69.2 ± 12.2	69.9 ± 13.3
Charlson Comorbidity Index			
Mean ± SD	3.30 ± 2.0	3.45 ± 1.8	3.66 ± 1.9
<7	2699(94.9%)	488(95.7%)	291(93.0%)
≧ 7	144(5.1%)	22(4.3%)	22(7.0%)
Location			
Right	749(26.3%)	75(14.7%)	59(18.8%)
Left	1124(39.5%)	214(42.0%)	109(34.8%)
Rectum	903(31.8%)	208(40.8%)	133(42.5%)
Multiple lesions	67(2.4%)	13(2.5%)	12(3.8%)
Emergency operation	97(3.4%)	30(5.9%)	19(6.1%)
Perforation	18(0.6%)	9(1.8%)	4(1.3%)
Obstruction	77(2.7%)	17(3.3%)	14(4.5%)
Bleeding	1(0.01%)	1(0.2%)	1(0.3%)
Simultaneous Stoma	487(17.1%)	151(29.6%)	83(26.5%)
Laparoscopy	333(11.7%)	44(8.6%)	26(8.3%)
Postop Treatment+	1057(37.2%)	181(35.5%)	103(32.9%)
Tumor size (mean ± SD)	4.4 ± 2.4	4.5 ± 2.2	4.8 ± 2.4
Lymph nodes harvest (mean ± SD)	17.7 ± 10.1	17.8 ± 9.8	17.3 ± 9.3
Stage			
1	662(23.3%)	122(23.9%)	60(19.2%)
2	1157(40.7%)	204(40.0%)	137(43.8%)
3	1024(36%)	184(36.1%)	116(37.1%)
Differentiated			
Well	133(4.7%)	19(3.7%)	18(5.7%)
Moderate	2486(87.4%)	446(87.5%)	273(87.2%)
Poor	161(5.7%)	30(5.9%)	16(5.1%)
Unknown	63(2.2%)	15(2.9%)	6(1.9%)
Microinvasion	383(13.5%)	74(14.5%)	50(16.0%)
Lymphatic invasion	320(11.3%)	64(12.5%)	44(14.1%)
Angioinvasion	129(4.5%)	31(6.1%)	21(6.7%)
Perineural invasion	84(3.0%)	23(4.5%)	11(3.5%)
Time to recurrence month (mean ± SD)	21.8 ± 17.8	21.9 ± 22.3	25.0 ± 20.1
Recurrence	295	76	54
Local recurrence	42(1.5%)	12(2.4%)	5(1.6%)
Distant metastasis	221(7.8%)	46(9.0%)	37(11.8%)
Local + Distant	32(1.1%)	18(3.5%)	12(3.8%)
Follow up months			
Mean	55.2 ± 34.9	64.0 ± 41.5	58.7 ± 45.9
Range	1~280	1-171	1-311

test. OS and DFS were analyzed using the Kaplan-Meier method. Variables with P<0.05 in univariate analyses were entered into the multivariate analysis, for which Cox proportional models were used to identify independent predictors of survival.

Results

Between January 1993 and December 2009, 4798 patients diagnosed with CRC underwent surgical resection at our institute.

Table 2: Complication Types and Severity Grade.

Complication type		Clavien-Dindo complication classification			
	Percent %	1	2	3	4
Wound infection	7.64	214	14	52	0
Anastomosis leakage	3.55	3	31	69	27
Ileus	3.43	65	16	33	12
Stroke	0.16	1	2	1	2
AMI	0.3	0	2	1	8
Congestive heart failure	0.22	0	3	0	5
Arrythmia	0.14	3	0	0	2
Atelectasis	0.16	3	3	0	0
Penumonia	1.28	1	18	1	27
Pneumothorax	0.03	0	1	0	0
Jaudice	0.19	1	3	2	1
UGI bleeding	0.22	0	7	1	0
DVT	0.16	0	6	0	0
Wound disruption	0.74	5	1	16	5
UTI	0.98	10	26	0	0
Urine retension	0.98	1	35	0	0
Intra abdominal abscess	0.3	0	6	5	0
Anastomosis bleeding	0.25	0	2	6	1
Intestinocutaneous fistula	0.25	0	1	6	2
Anovaginal fistula	0.16	0	1	5	0
Chronic perineal fistula	0.05	0	0	2	0
Ureteral injury	0.16	0	0	6	0
Incision hernia	0.33	3	0	9	0
Chyle leakage	0.6	9	9	4	0
Others	0.16	0	4	0	2

The perioperative mortality rate was 2.6%; additionally, our study excluded patients who died within 30 days of the primary operation (n=129). Patients with stage 0 (n=210) and stage IV (n=913) cancer, and those who received palliative resection (n=895) were also excluded from the analysis. Therefore, a total of 3 666 patients who underwent curative resection were included in the study (Figure 1).

A total of 823 patients developed complications, with an overall postoperative morbidity rate of 22.4%. Clinic pathological data of the patients are listed in Table 1. Notably, there were more male patients, rectal cancers, and higher Charlson Comorbidity Index and emergency operations in the complication group; additionally, less laparoscopy-assisted surgery and more simultaneous stoma creation were performed in the complication group. There were no significant differences between the two groups in tumor size, number of lymph nodes harvested, AJCC stage, tumor differentiation, or the presence of micro invasive carcinoma.

Table 2 summarizes the details of the complications. In the complication group, 313 patients (38.0%) had major and 510 patients (62.0%) had minor complications. Wound infection was the most common surgical complication (n=280, 7.64%), followed by anastomosis leakage (n=130, 3.55%). Postoperative ileus occurred in 82 patients (2.24%).

The mean follow-up duration was 55.2, 64.0, and 58.7 months in complication-free, minor complication and major complication groups, respectively (Table 1). There were 88 patients in the complication group and 362 patients in non-complication group who had lost of follow-up within two years, and the rates of loss of follow-up are 11% and 12.7% successively. There were 29 patients (9.3%) of the group with major complication, 59 patients (11.6%) of the group with minor complication and 362 patients (12.7%) of the group without complication lost to follow-up within 2 years after surgery (P=0.12). Of the 3 666 patients, 425 (11.6%) experienced recurrence; the mean time to recurrence was 22.2 months. Recurrence occurred in 54 patients in the major complication group, in 76 patients in the minor complication group and in 295 patients in the non-complication group (17.3% *vs*. 14.9% *vs*. 10.4%, P<0.001). Though more recurrence were observed in the complication group, the time to recurrence did not differ between the three groups (25.0 ± 20.1 months *vs*. 21.9 ± 22.3 months *vs*. 21.8 ± 17.8 months, P=0.501).

Table 3 shows the univariate and multivariate analyses for 5-year OS in patients with or without complications. According to the results of univariate analysis, the confounders including gender, age, Charlson Comorbidity Index, tumor location, emergency operation, simultaneous stoma creation, laparoscopy surgery, adjuvant treatment, AJCC stage, tumor size, lymph nodes harvest and micro invasive carcinoma were adjusted in multivariate analysis for estimating overall survival. A significantly worse 5-year OS

Table 3: Univariate (Cox Proportional Hazard Regression) and Multivariate (Cox Proportional Hazard Regression) Analysis of 5-Year Overall Survival (OS) in Patients with Minor complication, Major complication and Without Complications.

	Univariate	Multivariate	
	Hazard ratio	**Hazard ratio**	P
Complication Grade			
Non complication	1	1	
Minor complication	1.31(1.07-1.60)	1.21(0.98-1.48)	0.074
Major complication	2.03(1.65-2.51)	1.70(1.37-2.11)	0.001
Gender			
Male	1.41(1.20-1.66)	1.15(0.97-1.36)	0.114
Female	1	1	
Age			
<68	1	1	
≧ 68	2.23(1.89-2.64)	2.04(1.71-2.42)	0.001
Charlson Comorbidity Index			
<7	1	1	
≧ 7	1.50(1.26-1.78)	2.08(1.60-2.71)	0.001
Location			
Right	1	1	
Left	0.87(0.71-1.07)	0.91(0.74-1.12)	0.381
Rectum	1.18(0.97-1.44)	1.18(0.94-1.48)	0.151
Emergency			
No	1	1	
Yes	1.85(1.34-2.57)	1.39(0.99-1.96)	0.056
Simultaneous stoma			
no	1	1	
yes	1.52(1.28-1.80)	1.32(1.09-1.60)	0.004
Laparoscopy			
no	1	1	
yes	0.45(0.31-0.64)	0.55(0.38-0.79)	0.001
Postop treatment			
No	1	1	
Yes	1.27(1.09-1.48)	0.78(0.64-0.95)	0.012
AJCC Stage			
I	1	1	
II	1.18(0.94-1.48)	1.13(0.90-1.44)	0.293
III	2.19(1.77-2.71)	2.35(1.81-3.05)	0.001
Tumor size			
<5 cm	1	1	
≧ 5 cm	1.25(1.08-1.45)	1.25(1.06-1.46)	0.007
Lymph node harvest			
<18	1	1	
≧ 18	0.84(0.72-0.98)	0.81(0.69-0.96)	0.012
Microinvasion			
No	1	1	
Yes	2.20(1.85-2.62)	1.72(1.43-2.07)	0.001

Table 4: Univariate (Cox Proportional Hazard Regression) and Multivariate (Cox Proportional Hazard Regression) Analysis of 5-Year Disease-Free Survival (DFS) in Patients with Minor complication, Major complication and Without Complications.

	Univariate	Multivariate	
	Hazard ratio	**Hazard ratio**	**P**
Complication Grade			
Non complication	1	1	
Minor complication	1.50(1.16-1.93)	1.25(1.05-1.48)	**0.013**
Major complication	1.92(1.44-2.55)	1.63(1.34-1.97)	**0.001**
Gender			
Male	1.09(0.89-1.33)		
Female	1		
Age			
Age<68	1		
Age>68	1.00(0.85-1.18)		
Charlson Comorbidity Index			
<7	1	1	
≧ 7	1.98(1.55-2.53)	1.96(1.53-2.50)	**0.001**
Location			
Right	1	1	
Left	1.07(0.84-1.35)	0.92(0.82-1.17)	0.835
Rectum	1.50(1.20-1.88)	1.16(0.95-1.40)	**0.14**
Emergency			
No	1	1	
Yes	1.92(1.34-2.74)	1.51(1.12-2.04)	**0.006**
Simultaneous stoma			
no	1	1	
yes	1.96(1.64-2.34)	1.43(1.22-1.68)	**0.001**
Laparoscopy			
no	1	1	
yes	0.51(0.36-0.74)	0.62(0.47-0.82)	**0.001**
Postop treatment			
No	1	1	
Yes	2.24(1.90-2.65)	0.88(0.75-1.04)	0.133
Stage			
I	1	1	
II	2.03(1.50-2.74)	1.30(1.06-1.59)	**0.011**
III	4.16(3.12-5.53)	2.23(1.78-2.80)	**0.001**
Tumor size			
<5 cm	1	1	
≧ 5 cm	1.19(1.00-1.40)	1.09(0.92-1.24)	0.214
Lymph node harvest			
<18	1		
≧ 18	0.91(0.77-1.07)		
Microinvasion			
No	1	1	
Yes	2.12(1.75-2.58)	1.51(1.28-1.78)	**0.001**

was observed in the complication group, and OS was particularly low among patients with major complications (no complication *vs.* minor complication *vs.* major complication =86.1% *vs.* 79.4% *vs.* 69.3%, P<0.001, the numbers of event are 394, 105, and 96

Table 5: Influence of Major Complications on 5-Year Overall Survival and Disease-Free Survival in Different Stages.

		5-year Overall Survival(OS)			
		Univariate	**p**	**Cox regression (multivariate)**	**p**
Stage I	No complication	89.70%	0.4	1	
	Major complication	84.60%		1.385 (0.703~2.729)	0.35
Stage II	No complication	89.60%	<.001	1	
	Major complication	73.00%		2.272 (1.561~3.305)	<.001
Stage III	No complication	79.90%	<.001	1	
	Major complication	55.90%		2.187 (1.585~3.017)	<.001
		5-year Disease Free Survival(DFS)			
		Univariate	p	Cox regression (multivariate)	p
Stage I	No complication	86.60%	0.56	1	
	Major complication	83.10%		1.112 (0.588~2.103)	0.75
Stage II	No complication	83.40%	<.001	1	
	Major complication	65.70%		1.886 (1.363~2.611)	<.001
Stage III	No complication	71.20%	<.001	1	
	Major complication	47.70%		1.884 (1.410~2.517)	<.001

successively) (Figure 2). Similarly, the multivariate analysis revealed that the hazard ratio (HR) increases in the major complication group (HR=1.70, P=0.001). The other factors associated with an adverse 5-year OS included the age ≧ 68, Charlson Comorbidity Index ≧ 7, simultaneous stoma creation, open surgery, without adjuvant therapy, AJCC stage III cancer, the presence of micro invasive carcinoma, tumor size ≧5cm and lymph nodes harvest <18.

The univariate and multivariate analyses for 5-year DFS in patients with or without complications are summarized in Table 4. The confounders including Charlson Comorbidity Index, tumor location, emergency operation, simultaneous stoma formation, laparoscopy surgery, adjuvant treatment, AJCC stage, and tumor size and micro invasive carcinoma were entered into multivariate analysis according to the results in univariate analysis. A significantly worse 5-year DFS was observed in the complication group, and DFS was particularly low among patients with major complications (no complication *vs.* minor complication *vs.* major complication =79.7% *vs.* 71.1% *vs.* 62.9%, P<0.001, and the number of events are 576, 147, 116 successively) (Figure 3). The multivariate analysis revealed that the HR increases as the severity of the complications increases (HR=1.25, 1.63 in minor and major complication groups, respectively). The other factors associated with an adverse 5-year DFS included the Charlson Comorbidity Index ≧ 7, simultaneous stoma creation, an emergency operation, open surgery, AJCC stage II or III cancer, and the presence of micro invasive carcinoma.

Subsequently, we examined the influence of complication severity on long-term outcomes at different clinical stages. Minor complications posed no significant influence on 5-year OS or DFS in patients at any stage; conversely, major complications significantly reduced both OS and DFS in stage II and stage III patients (Table 5). However, the impact was not seen in stage I patients.

Discussion

This study consisted of the largest patient cohort from a single institute. The overall complication rate was 22.4%, which is lower than the results that have been reported in prior research and reflects the higher quality of care provided through our institute as a tertiary referral center [2,3,8,9]. Our data reveal that postoperative complications adversely affected the long-term outcomes of CRC patients who underwent curative resection, with the HR being approximately 1.5 for both OS and DFS, which is similar to that in a previous study [9]. Moreover, we demonstrated that adverse outcomes were related to the severity of the complications and the cancer stage of the patients; thus, stage II and III patients who experienced a major complication had the poorest OS and DFS outcomes.

Several studies have demonstrated significantly less favorable long-term outcomes in patients with postoperative complications after surgical resection for CRC with liver metastases [10-13]. However, studies investigating the impacts of complications after curative resection for stage I, II, and III CRC patients are sparse. Law et al. [3] demonstrated that postoperative complications significantly negatively affect the OS and overall recurrence rate in stage I to III CRC patients after curative resection. The study enrolled 1 657 patients from one hospital between 1996 and 2004; however, the complications were not stratified by severity. Odermatt et al. [8] reported significant effects of major complications on OS, but the same negative influence was not observed in the multivariate analysis for DFS; moreover, the total number of patients and the number of patients with complications were limited. Artinyan et al. [9] analyzed a large number of cases from a system-wide database of veterans in the United States and determined that complications, especially infectious complications, were related to poor OS. However, the database comprised male patients in a proportion greater than 90% and lacked detailed information on the complications; furthermore, the study did not explore disease recurrence. Conversely, our study comprises a large patient population with thorough information on postoperative complications after curative CRC surgery, and is the first to discuss the relationship between complication severity and long-term outcomes in patients at different clinical stages.

In our study, postoperative major complications had no significant impact on the long-term survival of stage I CRC patients. The OS and DFS did not differ between those with and those without major complications in stage I CRC patients (OS: 86.6% *vs.* 83%, P=0.22; DFS: 83% *vs.* 86.6%, P=0.28), which may be due to the less

or limited invasive nature of early-stage cancers. Moreover, the recurrence rate in these patients was low, limiting the influence of any complications on long-term outcomes. However, adverse effects of major complications were evident in both stage II and III patients. Similar results were observed by Khoury et al. [14], who reported lower 5-year OS and DFS rates in patients with complications that required early reoperation, which were classified as major complications in our study; additionally, Nachiappan et al. [15] reported anastomosis leakage that could be managed with conservative treatment was not an independent factor for poor long-term outcomes as well.

Other independent factors associated with poor DFS include old age, higher Charlson Comorbidity Index, simultaneous fecal diversion, open surgery, emergency operation, and micro invasive carcinoma. The complication group in this study consisted primarily of patients who were older, male, had higher Charlson Comorbidity Index score, rectal cancer and micro invasive carcinoma. All these factors had been reported to be associated with poor prognosis [16-19]. Additionally, more patients in the complication group underwent emergency surgery, which was also viewed as an independent predictor for adverse DFS in the study by Hogan et al. [20] The result that higher Charlson Comorbidity Index being significantly associated with poorer disease recurrence outcome after tumor resection were observed in various cancer including renal cell carcinoma, pancreatic cancer, breast cancer and hepatocellular carcinoma [21-25]. The adverse effects of increased Comorbidity burden and Charlson Comorbidity Index on the survival of patients with colon cancer were also stated in previous studies [26-28]. Ouellette JR et al. [16] reviewed 279 patients and divided the patients into two groups using Charlson Comorbidity Index score 7 as a cutoff based on the median of their dataset. They showed significant cancer-related survival advantage for Charlson Comorbidity Index score of 7 or less. 16 similarly, according to a review by Marventano Stefano, et al. [29], increased Charlson Comorbidity Index scores had an inferior cancer-specific survival and those with Charlson Comorbidity Index scores $\geqq$ 2 had about 1.6-fold increased risks of death [29]. The higher Charlson Comorbidity Index scores was found related to the postoperative complication in patients underwent colorectal cancer resection, and the poor outcome of patients with higher Charlson Comorbidity Index scores may attribute to this [30-32].

There were also more patients undergoing open surgery in the complication group. In a previous study, Wind et al. [19] detected significantly fewer circulating tumor cells during laparoscopic surgery; by contrast, Rahbari et al. [20] presented a meta-analysis that concluded that the detection of circulating tumor cells in the peripheral blood indicated poor prognosis in patients with primary CRC [33,34]. We argue that open surgery probably induced more tumor cells into circulation, which may be responsible for further metastasis. However, the impact of open surgery on long-term outcomes can be confounded by other factors, such as complicated lesions (e.g., large tumor size or locally advanced cancer) and an emergency requiring open surgery.

Previous studies investigating the influence of postoperative complications on the outcomes of patients with CRC, metastatic liver tumors, lung tumors, and gastric tumors have indicated that complications increase the risk of tumor recurrence [3-9,12,13]. Proposed mechanisms for this increase include a period of immune suppression, possibly caused by a systemic inflammatory response, following postoperative complications. Particularly after major complications, the possible reoperation and critically ill status can induce the systemic inflammatory response, which was likely correlated with a temporarily immune compromised system [35,36]. Prior research has also suggested that the presentation of cytokines and the subsequent down regulation of antigen-presenting cells play a key role in metastasis [37,38]. Other studies have revealed that bacterial antigen-mediated processes increase cell adhesion and metastasis [39,40]. Consequently, the immune suppression status induced through complications might not only break the resistance to spreading tumor cells but also promote tumor recurrence. These findings can facilitate explaining why minor complications do not affect patient outcomes. Specifically, the systemic inflammatory response following minor complications may be limited and not reach the threshold that affects outcomes.

Another important issue raised by Krarup et al. [41] is the complete omission of adjuvant therapy, which is another potential reason for poor prognosis in the complication group. However, in our study, the percentage of patients who underwent adjuvant therapy did not differ between the three groups significantly (major complication *vs*. minor complication *vs*. no complication =32.9% *vs*. 35.5% *vs*. 37.2%, P=0.284).

There are limitations in this study. First, the starting date of adjuvant therapy was not specified in the database; therefore, the effect of delayed adjuvant chemotherapy could not be assessed. It is quite common that adjuvant therapy is delayed by the occurrence of complications, which may be attributed to the unfavorable outcomes in the patients with complication as well [41]. Second, this is a retrospective study, and the complications recorded were obtained by the chart review. Some minor complications, such as wound infection or urinary tract infection, may be omitted in the discharge diagnosis. Therefore, the impact of minor complication could be difficult to evaluate.

Postoperative complications after curative resection for CRC had adverse effects on not only long-term OS but also DFS. The poor outcomes were related to the severity of the complications and the cancer stage of the patients, with stage II and III patients who experienced major complications after surgery having the poorest OS and DFS outcomes.

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