Postoperative Complications Predict Long-term Outcome After Curative Resection for Perforated Colorectal Cancer

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Abstract. *Background/Aim:* Perforation and postoperative complications have a negative effect on long-term outcomes in patients with colorectal cancer (CRC). The aim of this study was to evaluate the clinical factors with special reference to postoperative complications predicting the long-term outcome in those for whom curative resection for perforated CRC was performed. *Patients and Methods:* Patients who underwent curative resection for perforated CRC at stage II or III from April 2003 to March 2020 were included. Clinical factors were retrospectively analyzed. *Results:* Forty-four patients met the selection criteria. The 30-day mortality rate was 4.5% and the complication rate was 47.7%. Excluding 30-day mortality, five-year recurrence-free survival (RFS) and overall survival (OS) were 62.3% and 73.6%, respectively. Multivariate analysis showed that postoperative complications ($p=0.005$) and pT4 pathological factor ($p=0.009$) were independent prognostic factors for RFS. Only postoperative complications ($p=0.023$) were an independent prognostic factor for OS. *Conclusion:* Postoperative complications were significantly associated with RFS and OS, and pT4 was associated with RFS. The prevention and management of postoperative adverse events may be important for perforated CRC.

Perforated colorectal cancer (CRC) is complicated by both septic and oncological problems. Fecal leakage causes peritonitis, and in many cases emergent surgical procedures are required (1). In addition, extensive lymph node dissection is also necessary (2). After recovering from sepsis, patients

confront both a high rate of recurrence and poor survival. The long-term outcome of perforated CRC patients was reported to be poor compared with CRC without perforation (2-6).

Postoperative complications reportedly result in poor outcomes after resection of CRC (7, 8). Adjuvant chemotherapy is recommended for stage III and high-risk stage II disease (9); however, postoperative complications lead to delays in adjuvant chemotherapy (10). The prognostic factors that affect long-term survival and recurrence after curative resection for perforated CRC are unclear. Furthermore, the relationship between postoperative complications and long-term outcome has been rarely reported.

The aim of this study was to review clinical data of perforated CRC and evaluate various clinical factors with special reference to postoperative complications predicting the long-term outcome of patients who underwent curative resection for perforated CRC.

Patients and Methods

We performed a retrospective review of medical records of consecutive patients who underwent primary curative tumor resection for perforated CRC from April 2003 to March 2020 at Sasebo City General Hospital. Patients who experienced perforation after intubation of a transanal drainage tube ($n=11$), from a self-expandable metallic stent ($n=2$), during colonoscopy ($n=2$), or during chemotherapy ($n=2$), or who had appendiceal cancer perforation ($n=2$) were excluded. Only adenocarcinomas were included. Finally, 44 patients were included in the analysis. This retrospective study was approved by the institutional review board of the participating hospital, and informed consent was waived. The ethics approval number was 2020-A019.

We reviewed and recorded the following data: sex, age, American Society of Anesthesiologists Physical Status (ASA-PS), tumor location, presence or absence of emergent surgery, site of perforation, type of surgery, extent of lymph node dissection, histological type, pathological T stage, pathological N stage, lymphovascular invasion, number of dissected lymph nodes, postoperative complications, adjuvant chemotherapy, local recurrence, distant metastasis, and survival time.

The tumor stage was classified according to tumor-node-metastasis (TNM) classification (11). Postoperative complications

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Key Words: Colorectal cancer, colorectal cancer perforation, intestinal perforation.

Table I. Clinical characteristics of perforated colorectal cancer patients.

Number	44
Gender, male	19 (43.2)
Age (years, range)	76 (42-88)
ASA PS	
I-II	26 (59.1)
III-IV	18 (40.9)
Location of tumor	
Cecum	3 (6.8)
Ascending colon	4 (9.1)
Transverse colon	5 (11.4)
Descending colon	0 (0.0)
Sigmoid colon	24 (54.5)
Rectum	6 (13.6)
Site of perforation	
Proximal site	13 (29.5)
Cancer site	31 (70.5)
Emergent surgery	35 (81.8)
Treatment	
Resection and stoma construction	25 (56.8)
Resection+anastomosis with temporary stoma	2 (4.5)
Resection+anastomosis without temporary stoma	17 (38.6)
30 days mortality	2 (4.5)
Pathologic status	
Well differentiated	19 (43.2)
Moderately differentiated	22 (50.0)
Poorly differentiated	2 (4.5)
Mucinous	1 (2.3)
Pathological T stage	
pT1-pT2	0 (0.0)
pT3	25 (56.8)
pT4	19 (43.2)
Stage	
Stage II	33 (75.0)
Stage III	11 (25.0)
Lymphovascular invasion	
Negative	9 (20.5)
Positive	35 (79.5)

Data are number (%) or medians (range). ASA-PS; The American Society of Anesthesiologists Physical Status; CD, Clavien-Dindo classification.

were defined as complications that occurred within 30 days of the primary surgery. Patients with Clavien-Dindo grade 2 or higher complications were included in the complications group (12). Tumor location was classified as colon (cecum to rectosigmoid colon) and rectum. The site of perforation was divided into two groups: perforation of normal mucosa at the proximal side of the tumor and cancer site perforation (13).

Statistical analyses were performed using Bell Curve for Excel software, version 2.02 (Social Survey Research Information Co., Ltd., Tokyo, Japan). The data are presented as median values with ranges. Continuous data were compared using the Student's *t*-test, and categorical data were compared using Fisher's exact test or the chi-squared test, as appropriate. Five-year recurrence-free survival (RFS) and overall survival (OS) were calculated according to the Kaplan-Meier method. Patients who died within 30 days after surgery were excluded from the analysis of long-term outcomes. OS

Table II. Postoperative complications (CD grade 2-5).

Postoperative complication (CD Grade 2-5)	
Yes	21 (47.7)
No	23 (52.3)
Specific complications	
CD Grade 2	10 (22.7)
Wound infection	6 (13.6)
Prolonged ileus	4 (9.1)
Heart failure	1 (2.3)
CD Grade 3	8 (18.2)
Intraabdominal abscess	4 (9.1)
Wound infection	2 (4.5)
Stoma necrosis	1 (2.3)
Pneumonia	1 (2.3)
CD Grade 4	1 (2.3)
Prolonged sepsis	1 (2.3)
CD Grade 5	2 (4.5)
Prolonged sepsis	2 (4.5)

CD, Clavien-Dindo classification.

was defined as the duration from surgery to death or last follow-up. RFS was defined as the duration from surgery to cancer recurrence.

Multivariate analysis using a Cox hazards model was performed to identify the independent risk factors for OS. All variables related to the risk of RFS or OS with a *p*-value <0.10 on univariate analysis were included in the multivariate analysis. All *p*-values of <0.05 were considered significant.

Results

Table I shows the clinicopathological characteristics of 44 patients. The study population included 19 male (43.2%) and 25 female (56.8%) patients, with a median age of 76 (range=42-88) years. Among these patients, 18 (42.9%) had a poor performance status (ASA-PS≥3). Most had colon cancer (n=38, 86.4%), and sigmoid colon cancer accounted for the majority of patients. Thirteen patients (29.5%) had the perforation site at the oral site of the cancer and the rest experienced perforation at the cancer site. Most patients (n=35, 81.8%) underwent emergent surgery defined as surgery performed within 24 hours from hospital admission. Twenty-five patients (56.8%) underwent tumor resection and stoma construction. Two patients (4.5%) underwent resection and anastomosis with temporary stoma construction and 17 patients (38.6%) received resection without stoma construction. Histopathologically, 19 patients (43.2%) were diagnosed as pathological T4 (pT4). Eleven (25.0%) patients had stage III disease (25.0%). Most patients had lymphovascular invasion (n=35, 79.5%). Thirty-day mortality was 4.5% (n=2). Eighteen patients (40.9%) received adjuvant chemotherapy.

Table II shows the postoperative complications. The overall postoperative complication rate (CD≥2) was 47.7% (n=21).

Figure 1. Recurrence-free survival (RFS) estimates (a), according to the presence or absence of postoperative complications (b), and pT1-3 vs. pT4 (c).

Among 21 patients with morbidities, 10 (22.7%) had grade II complications, including wound infection (n=6, 13.6%), prolonged ileus (n=4, 9.1%), and heart failure (n=1, 2.3%). Eight patients (18.2%) had grade III complications, including intraabdominal abscess (n=4, 9.1%), wound infection (n=2, 4.5%), stoma necrosis (n=1, 2.3%), and pneumonia (n=1, 2.3%). One patient (2.3%) had grade IV prolonged sepsis and two patients (4.5%) experienced postoperative death within 30 days related to prolonged sepsis (grade V).

Table III shows the clinical differences between patients with and without postoperative complications. There were no significant differences in sex, age, ASA-PS, emergent surgery, site of perforation, type of surgery, pathological T stage, stage, and adjuvant chemotherapy. The rate of rectal cancer was higher in the postoperative complications group.

Among 42 patients, excluding two patients who experienced 30-day mortality, the median follow-up period of the present study was 41 months (range=0-190 months).

Thirteen patients experienced recurrence including peritoneal dissemination (n=4), liver metastasis (n=3), lung metastasis (n=3), lymph node metastasis (n=2), and ovarian metastasis (n=1). The 5-year actuarial RFS was 62.3% (Figure 1a). RFS was poor in the postoperative complications group ($p=0.006$; Figure 1b) and in pT4 patients ($p=0.034$; Figure 1c). Table IV shows the results of univariate and multivariate analyses of risk factors for RFS. Postoperative complications ($p=0.027$) and pT4 ($p=0.046$) were significantly associated with RFS on univariate analysis. Multivariate analysis showed that postoperative complications (OR=5.720; 95% CI=1.695-19.305; $p=0.005$) and pT4 (OR=5.226; 95% CI=1.518-18.000; $p=0.009$) were independent prognostic factors for RFS.

The 5-year OS was 73.6% (Figure 2a). OS was poor in the postoperative complications group ($p=0.019$; Figure 2b) and in patients who did not receive adjuvant chemotherapy ($p=0.016$; Figure 2c). Table V shows the results of univariate

Figure 2. Overall survival (OS) estimates (a), according to the presence or absence of postoperative complications (b), and by the presence or absence of adjuvant chemotherapy (c).

and multivariate analyses of risk factors for OS. Postoperative complications ($p=0.034$) and adjuvant chemotherapy ($p=0.044$) were significantly associated with OS on univariate analysis. Multivariate analysis showed that only postoperative complications ($OR=6.627$; 95% $CI=1.304-33.683$, $p=0.023$) was an independent prognostic factor for OS.

Discussion

This single center retrospective study investigated the long-term outcomes of perforated CRC patients who underwent primary curative tumor resection. Postoperative complications and pT4 were independent risk factors for poor RFS. Furthermore, postoperative complications were an independent risk factor for poor OS.

Perforated CRC patients face the life-threatening conditions of both malignant disease and sepsis (1). These patients often

require emergent surgery (1), with perioperative mortality ranging between 11%-21% (13-18). Furthermore, even after perforated CRC patients recover from peritonitis and the perioperative phase, colorectal perforation is reported to be a risk factor for poor prognosis (2-5) and high recurrence (3, 6). This high recurrence rate is reported to be associated with the dissemination of cancer cells due to perforation and reduced lymph node dissection (13).

Postoperative complications after resection of CRC have been reported to be a factor associated with worse survival and a higher recurrence rate (7, 8) and the relationship between postoperative complications after curative perforated CRC and long-term outcome have been rarely reported.

In the current study, the rate of postoperative complications was 47.7% and included eight cases of wound infection, eight cases of intraabdominal complications including stoma, and five cases associated with general condition. Although the severity of the tumor and the general

Table III. Comparison of clinical characteristics between perforated colon cancer patients with postoperative complications (CD ≥ 2) and without postoperative complications (CD < 2).

	Postoperative complications (+) (n=21)	Postoperative complications (-) (n=23)	p-value
Gender			0.361
Male	11 (52.4)	8 (34.8)	
Female	10 (47.6)	15 (65.2)	
Age (median, range)	76 (42-78)	71 (45-87)	0.509
ASA-PS			0.541
I-II	11 (52.4)	15 (65.2)	
III-IV	10 (47.6)	8 (34.8)	
Location of tumor			0.042
Colon	15 (71.4)	22 (95.7)	
Rectum	6 (28.6)	1 (4.3)	
Emergent surgery			0.701
Yes	18 (85.7)	18 (78.3)	
No	3 (14.3)	5 (21.7)	
Site of perforation			0.130
Proximal site	8 (38.1)	15 (65.2)	
Cancer site	13 (61.9)	8 (34.8)	
Type of surgery			>.999
Anastomosis (+)	9 (42.9)	10 (43.5)	
Anastomosis (-)	12 (57.1)	13 (56.5)	
Pathological T stage			0.557
pT1-3	13 (61.9)	12 (52.2)	
pT4	8 (38.1)	11 (47.8)	
Stage			0.303
Stage II	7 (33.3)	4 (17.4)	
Stage III	14 (66.7)	19 (82.6)	
Lymphovascular invasion			>.999
Yes	17 (81.0)	18 (78.3)	
No	4 (19.0)	5 (21.7)	
Adjuvant chemotherapy			0.136
Yes	6 (28.6)	12 (52.2)	
No	15 (71.4)	11 (47.8)	

ASA-PS, The American Society of Anesthesiologists Physical Status; CD, Clavien-Dindo classification.

performance status could affect the long-term outcome, excluding two cases of postoperative mortality, there was no difference between with or without complications except for the location of the tumor.

Adjuvant chemotherapy is recommended for stage III and high-risk stage II disease, including perforated CRC patients (9). Meanwhile, postoperative complications are associated with delays in adjuvant chemotherapy (10) and these delays lead to worse RFS and OS (19). In this study, there was no difference in RFS and OS between the cases with and without adjuvant chemotherapy on multivariate analysis; however, the delay in postoperative chemotherapy tended to be more than 8 weeks in the postoperative group (3/6 (50%) vs. 1/12 (8.3%); $p=0.080$). This delay in adjuvant chemotherapy might have affected the long-term outcome.

Table IV. Clinical factors predicting RFS after curative resection of perforated colorectal cancer.

	Univariate analysis	Multivariate analysis		
	p-Value	HR	95%CI	p-Value
Gender	0.746			
Male				
Female				
Age, years	0.778			
≥ 70				
< 70				
ASA-PS	0.346			
1-2				
≥ 3				
Tumor location	0.934			
Colon				
Rectum				
Emergent surgery	0.768			
Yes				
No				
Site of perforation	0.365			
Tumor				
Oral				
Central node dissection	0.116			
Yes				
No				
Lymph node sampled	0.706			
≥ 12				
< 12				
Pathological T stage	0.046			0.009
pT1-3		1		
pT4		5.226	1.518-18.000	
Stage	0.408			
I-II				
III				
Lymphovascular invasion	0.462			
Yes				
No				
Postoperative complication (CD ≥ 2)	0.027			0.005
Yes		5.720	1.695-19.305	
No		1		
Adjuvant chemotherapy	0.854			
Yes				
No				

HR, Hazard ratio; CI, confidence interval; ASA-PS, The American Society of Anesthesiologists Physical Status; CD, Clavien-Dindo classification.

The results of our study suggest that complications of surgery for perforated CRC may affect both short- and long-term cancer outcomes. This research also revealed that pT4 is associated with the high recurrence rate. Previous research revealed several risk factors for the long-term outcome of perforated CRC. Lymph node metastasis (3, 14) and oral site perforation, compared with cancer site

Table V. Clinical factors predicting OS of curative resection of perforated colorectal cancer.

	Univariate analysis	Multivariate analysis	
	p-Value	HR	95%CI
Gender	0.534		
Male			
Female			
Age, years	0.124		
≥70			
<70			
ASA-PS	0.054		0.141
1-2		1	
≥3		3.016	0.693-13.125
Tumor location	0.574		
Colon			
Rectum			
Emergent surgery	0.612		
Yes			
No			
Site of perforation	0.547		
Tumor			
Oral			
Central node dissection	0.569		
Yes			
No			
Lymph node sampled	0.699		
≥12			
<12			
Pathological T stage	0.141		
T1-3			
T4			
Stage	0.929		
I-II			
III			
Lymphovascular invasion	0.445		
Yes			
No			
Postoperative complication (CD≥2)	0.034		0.023
Yes		6.627	1.304-33.683
No		1	
Adjuvant chemotherapy	0.044		0.143
Yes		1	
No		3.016	0.693-13.125

HR, Hazard ratio; CI, confidence interval; ASA-PS, The American Society of Anesthesiologists Physical Status; CD, Clavien-Dindo classification.

perforation (14), were reported to be risk factors for poor OS and RFS. Insufficient lymph node dissection (2), pathological stage (20), and free perforation compared to contained perforation (18), were reported to be associated with poor OS. Although perforated CRC requires a short surgical time from the viewpoint of emergent surgery with sepsis, extensive lymph node dissection is required to

improve the long-term outcome. In these years the long-term outcome of colorectal cancer is reported to be poor in right-sided cancer compared to left-sided (21). In this study, there was no statistical differences in 5-year OS (right-sided, 77.8% vs. left-sided, 71.8%; $p=0.910$) and RFS (right-sided, 63.5% vs. left-sided, 62.2%; $p=0.883$). Regarding anastomosis, primary anastomosis with or without ileostomy was reported to be equivalent in perforated diverticulitis, but not cancer perforation (22). The safety of primary anastomosis for perforated CRC is controversial. Thus, simple surgical procedures should be considered to reduce postoperative complications and to prevent a delay in adjuvant chemotherapy.

Regarding strengths and weaknesses of this study, the present study had several limitations. First, relatively few patients were evaluated and the study design was retrospective. Because of the low incidence of the disease, reportedly 2.6-10% among CRC patients (1), it is hard to recruit many patients. Further prospective studies in larger cohort are needed to further confirm our results. Second, the surgical procedure and induction of postoperative adjuvant chemotherapy were dependent on the surgeons and cases. Third, there might be a time bias as the data in this study were collected over a relatively long period. During this time, the surgical procedures and postoperative treatment might have changed.

The strength of this study is that our cohort included only consecutive patients who experienced curative resection for perforated CRC. Long-term outcome and the analysis of the risk factor of poor OS and RFS after resection for perforated CRC is limited and this result can be a valuable report.

In conclusion, postoperative complications and pT4 were associated with RFS, and postoperative complications also increased the risk of poor OS. The prevention and management of postoperative adverse events may be important to improve RFS and OS for perforated CRC.

Conflicts of Interest

None of the Authors has any financial interest related to this study.

Authors' Contributions

Shintaro Hashimoto and Kiyoaki Hamada were responsible for the study concept. Shintaro Hashimoto, Kiyoaki Hamada, Araki Masato, Yori-hisa Sumida, Koki Wakata, Tota Kugiyama, Ayako Sibuya, Masato Nishimuta, Shigeyuki Morino, Masayuki Baba, Soichiro Kiya, and Keisuke Ozeki collaborated in the patients' medical care. Yori-hisa Sumida and Akihiro Nakamura reviewed the manuscript. All Authors approved the final article.

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