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CLINICOPATHOLOGICAL OUTCOMES AND RISK FACTORS FOR POSTOPERATIVE RECURRENT AND HOSPITAL MORTALITY IN PATIENTS WITH PERFORATED COLORECTAL CANCER

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Abstract – *Objective:* *Even after surgery and intensive postoperative treatment, the mortality rate of patients with perforated colorectal cancer (CRC) is high. The purpose of this retrospective study was to evaluate risk factors for postoperative recurrence and hospital mortality in patients with perforated CRC.*

Patients and Methods: *We experienced a total of 142 patients who were diagnosed with colorectal perforation and who underwent emergency surgery from 2008 to 2021. First, we performed a clinicopathological study of patients with perforated CRC. Next, we examined the clinicopathological characteristics of the CRC and non-CRC groups. We investigated the histopathological characteristics and risk factors for postoperative recurrence and hospital mortality in 32 patients with perforated CRC.*

Results: *The Hinchey stage of the CRC group was significantly higher than that of the non-CRC group (p=0.00619), and that in the proximal site group was significantly higher than that of the cancer site group (p=0.00489). The rate of recurrence in the proximal site perforation group was significantly higher than that in the cancer site perforation group (p=0.0135). Patients with T4 disease showed a significantly higher rate of recurrence than those with T3 disease (p=0.0443). The number of dissected lymph nodes in the recurrence-free group was significantly higher than that in the recurrence group (p=0.0377). There was a tendency for more patients in the recurrence-free group to receive postoperative adjuvant chemotherapy; however, this difference was not statistically significant. The preoperative shock rate in the hospital mortality group was significantly higher than that in the alive at discharge group (p=0.0169).*

Conclusions: *The proximal site perforation, T4 disease, and the small number of dissected lymph nodes were the risk of the recurrence. The large number of preoperative shocks was the risk of the hospital mortality.*

KEYWORDS: *Perforation, Colorectal cancer, Recurrence, Adjuvant chemotherapy, Hospital mortality.*

INTRODUCTION

Because colorectal perforation causes widespread dissemination of bacteria throughout the intra-abdominal space, severe bacterial infection can easily lead to septic shock, and the disease is likely to rapidly become severe. Once the disease becomes severe, it leads to disseminated intravascular coagulation (DIC) and multiple organ failure (MOF), a condition associated with a

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mortality rate of 12-26% in modern medicine[1-7]. To improve the survival rate, it is important to accurately assess the patient's general condition and preoperative risk factors for mortality, and to apply appropriate surgical indications and procedure selection with subsequent intensive care. On the other hand, colorectal cancer (CRC) is a frequent cause of colorectal perforation, and in many cases, perforation occurs in patients with an advanced stage of disease and is associated with a poor prognosis. However, perforation in patients with CRC confers a risk of postoperative recurrence due to the malignant nature of the disease. Furthermore, the recurrence rate is higher in patients with CRC than in those who have undergone elective surgical treatment for CRC[8-10]. This is because patients with perforated CRC are prone to peritoneal recurrence due to the spread of cancer cells from the perforation site into the peritoneal cavity[11]. In addition, since patients with perforated CRC have advanced cancer, the perforation may cause peritonitis, which may reduce the systemic immune capacity and lead to distant metastasis to the liver and lungs[12]. To improve the prognosis of patients with perforated CRC, it seems important to explore the risk factors for recurrence. In the present study, we aimed to clarify the clinical characteristics of patients with colorectal perforation, and to determine the characteristics of patients with perforated CRC by comparing the characteristics of patients with and without CRC. We investigated the risk factors for the recurrence of perforated CRC and how to improve the prognosis. In addition, we analyzed the risk factors for hospital mortality and investigated appropriate treatments.

PATIENTS AND METHODS

Patients

We experienced a total of 142 patients who were diagnosed with colorectal perforation and who underwent emergency surgery from 2008 to 2021. Among them, 32 patients with colorectal perforation caused by CRC were investigated. We excluded cases of perforation of the appendix and cases of perforation due to suture failure in patients who received colorectal surgery.

Methods

First, we performed a clinicopathological study of patients with perforated CRC. Next, we examined the clinicopathological characteristics of the perforated CRC and non-CRC groups. The preoperative data gathered included: age, sex, perforation site, Hinchey stage, operation time, time to operation from onset of symptoms, presence of preoperative shock (systolic pressure <80 mmHg), the sequential organ failure assessment (SOFA) score[13], and hospital mortality. In addition, the sites of perforation were classified into two groups (the cancer site group and the proximal site group), and a clinicopathological comparison was performed. In terms of postoperative recurrence, we divided the patients into two groups, the recurrence group and the recurrence-free group, and compared their clinicopathological factors. Patients with perforated CRC were classified into two groups: the hospital mortality group and the alive at discharge group, and risk factors for hospital mortality were investigated. Finally, we compared overall survival rates according to stage and site of perforation (cancer site, proximal site).

Evaluations

Regarding the extent of lymph node (LN) dissection in CRC patients, the Japanese guidelines[14] stipulate a standard regional dissection involving the intermediate and main lymph nodes. Disease stages were determined according to the 8th UICC[15]. Patient background characteristics, surgical findings, histopathological findings, postoperative course, and distant results were reviewed.

All procedures were in accordance with the Ethical Standards of the Responsible Committee on Human Experimentation (institutional and national) and with the 1964 Declaration of Helsinki and later versions. This study was approved by the Ethics Committee of Mitoyo General Hospital (approval number: 21-CR01-185; approval date, December 19, 2021).

Statistical Analysis

Statistical analyses were performed using IBM SPSS 24 package program (SPSS Inc., Armonk, NY, USA). The chi-square and Fisher's exact tests were used to compare categorical variables, and Student's *t*-test or the Mann-Whitney test was used to compare continuous variables. The overall survival was calculated using the Kaplan-Meier method, and differences in survival were determined by using the log-rank test. All tests were two-sided and values of <0.05 were considered statistically significant.

RESULTS

The mean age was 75.7 years old, and there were 19 males and 13 females.

The most common site of perforation was the sigmoid colon (n=18; 56.3%), followed by the rectum (n=7), transverse colon (n=3), cecum (n=3), ascending colon (n=1), and descending colon (n=1). Twenty patients had proximal site perforation and 12 had cancer site perforation. The most common treatment was primary resection without anastomosis (n=21; 65.6%)), followed by primary resection with anastomosis (n=8), drainage without resection (n=2), and second stage operation (n=1). Surgery-related mortality rate was 6.3% (n=2) and the hospital mortality rate was 15.6% (n=5).

The most common histological type was the moderately differentiated type (tub2) (n=16; 50%), followed by well differentiated type (tub1) (n=9), mucinous adenocarcinoma (muc) (n=3), and papillary adenocarcinoma (pap) (n=1). The pathological stage was stage II in 10 patients, stage III in 8, and stage IV in 9 (Table 1).

TABLE 1. Clinicopathological characteristics of patients with perforated CRC.

Clinicopathological characteristics (n=32)	*Number (%)*
Age (years)	75.7 (44-99)
Sex (male/female)	19/13
Location of tumor	
Cecum	2 (6.3%)
Ascending colon	1 (3.1%)
Transverse colon	3 (9.4%)
Descending colon	1 (3.1%)
Sigmoid colon	18 (56.3%)
Rectum	7 (21.9%)
Perforation site	
Cancer site	12 (37.5%)
Proximal site	20 (62.5%)
Treatment	
Primary resection without anastomosis	21 (65.6%)
Primary resection with anastomosis	8 (25%)
Drainage without resection	2 (6.3%)
Second stage	1 (3.1%)
Surgery-related mortality	2 (6.3%)
Hospital mortality	5 (15.6%)
Macroscopic classification	
Type 2	20 (62.5%)
Type 3	9 (28.1%)
Unknown	3 (9.4%)
Histological type	
tub1	9 (28.1%)
tub2	16 (50%)
pap	1 (3.1%)
muc	3 (9.4%)
Unknown	3 (9.4%)
T factor	
T3	17 (53.1%)
T4a	9 (28.1%)
T4b	6 (18.8%)
N factor	
N0	10 (31.3%)
N1	12 (37.5%)
N2	1 (3.1%)
Unknown	9 (28.1%)
Stage	
II	10 (31.3%)
III	8 (25%)
IV	9 (28.1%)
Unknown	5 (15.6%)

tub1: well differentiated type; tub2: moderately differentiated type; pap: papillary adenocarcinoma; muc: mucinous adenocarcinoma

Clinicopathological characteristics of the CRC and non-CRC groups

There were 32 patients in the CRC group and 110 patients in the non-CRC group. There were no significant differences between the two groups with respect to age, sex, perforation site, operation time, time to operation from the onset of symptoms, presence of preoperative shock (systolic pressure <80 mmHg), sequential organ failure assessment (SOFA) score, and hospital mortality. The Hinchey stage of the CRC group was significantly higher than that of the non-CRC group (p= 0.00619) (Table 2).

Clinicopathological characteristics of the sites of perforation in the cancer site and proximal site groups

The CRC patients were divided into two groups, the cancer site group (n=12) and proximal site group (n=20), according to the site of perforation and their clinicopathological characteristics were compared. There were no significant differences between the two groups with respect to the macroscopic classification, histological type, T factor, N factor, pathological stage, time to operation from the onset of symptoms, and hospital mortality. The Hinchey stage of the proximal site group was significantly higher than that of the cancer site group (p=0.00489). The most common site of recurrence was the peritoneum in both groups (Table 3).

Clinicopathological characteristics of patients with and without recurrence

After excluding patients with stage IV disease or an unknown disease stage, the 17 patients who could be followed up were divided into two groups, the recurrence group (n=9) and the recurrence-free group (n=8), and their clinicopathological characteristics were compared. There were no significant

TABLE 2. Clinicopathological characteristics of CRC and non-CRC groups.

	Cancer group (n=32)	Non-cancer group (n=110)	p-value
Age (years)	75.7±11.8	75.0±14.2	0.756
Sex			0.159
Male	19	49	
Female	13	61	
Site of perforation			0.532
Cecum	2	1	
Ascending colon	1	5	
Transverse colon	3	7	
Descending colon	1	6	
Sigmoid colon	18	75	
Rectum	7	16	
Hinchey stage			0.00619
1	8	44	
2	0	8	
3	14	18	
4	10	40	
Operation time (min)	150.5±48.3	136.5±44.1	0.162
Time to operation from onset of symptoms (hours)	21.6±30.7	22.9±32.3	0.114
Preoperative shock			0.659
Yes	2	12	
No	30	98	
SOFA score	1.56±1.5	1.73±2.0	0.695
Hospital mortality			0.679
Yes	5	12	
No	27	98	

Mean±standard deviation, SOFA: Sequential Organ Failure Assessment.

differences between the two groups with respect to the macroscopic classification, histological type, T factor, N factor, and pathological stage. Proximal site recurrence was observed significantly more frequently than recurrence at the cancer site (p=0.0135). In addition, in patients with recurrence, T4 disease was observed significantly more frequently than T3 disease (p=0.0443). The number of dissected lymph nodes was significantly higher in the recurrence-free group than in the recurrence group (p=0.0377). With regard to postoperative adjuvant chemotherapy, the recurrence-free group tended to receive adjuvant chemotherapy more frequently; however, this difference was not statistically significant (Table 4).

Clinicopathological characteristics of the hospital mortality group and the alive at discharge group

We compared the clinicopathological results of the hospital mortality group (n=5) and the alive at discharge group (n=27). There were no significant differences between the groups in terms of age, sex, site of perforation, perforation site (cancer site or proximal site), pathological stage, Hinchey stage, operation time, time to operation from the onset of symptoms, and SOFA score. The frequency of preoperative shock was significantly higher in the hospital mortality group than in the alive at discharge group (p=0.0169) (Table 5).

Overall survival

A significant difference was observed in the 5-year overall survival rates of the stage II and stage IV groups (p=0.029). In contrast, the 5-year overall survival rates of the stage II and stage III groups did not differ to a statistically significant extent (Figure 1). Furthermore, the 5-year overall survival rates of the cancer site perforation and proximal site perforation groups did not differ to a statistically significant extent (Figure 2).

TABLE 3. Clinicopathological characteristics of the cancer site perforation group and the proximal site perforation group.

	Cancer site group (n=12)	*Proximal site group (n=20)*	*p-value*
Macroscopic classification			0.351
Type 2	8	12	
Type 3	2	7	
Unknown	2	1	
Histological type			0.358
tub1	2	7	
tub2	5	11	
pap	1	0	
muc	2	1	
Unknown	2	1	
T factor			0.257
T3	5	12	
T4a	3	6	
T4b	4	2	
N factor			0.191
N0	3	7	
N1	4	6	
N2	0	1	
Unknown	5	6	
Stage			0.541
II	3	7	
III	1	5	
IV	4	5	
Unknown	4	3	
Recurrent site*			
Peritoneum	1	6	
Liver	0	4	
Lung	1	3	
Local	0	2	
Hinchey stage			0.00489
1	3	5	
2	0	0	
3	9	5	
4	0	10	
Time to operation from onset of symptoms (hours)	23.2±33.2	20.7±29.9	0.292
Hospital mortality	1 (8.3%)	4 (20%)	0.615

tub1: well differentiated type, tub2: moderately differentiated type, pap: papillary adenocarcinoma, muc: mucinous adenocarcinoma Mean±standard deviation, Recurrent site*: there are duplicates.

DISCUSSION

Severe colorectal perforation has a poor prognosis and can easily lead to sepsis, DIC, and MOF due to generalized peritonitis. In the past, the mortality rate was reported to be 12-26% even after immediate treatment with emergency surgery[3,6,16-19]. The prediction of mortality using routinely, and easily available preoperative parameters is important for providing adequate information about the likelihood of postoperative death to patients and their families and to prepare for intensive postoperative management should the need for rescue arise. If the patient recovers from severe disease, long-term survival can be expected because of the disease is benign. However, in the case of perforated CRC, even if the patient recovers from the acute phase, they may have distant metastasis or postoperative recurrence, which require treatment.

The Hinchey stage of patients with perforated CRC was significantly higher in comparison to the non-CRC group. One of the reasons for this was that the non-CRC group included 9 cases of

TABLE 4. Clinicopathological characteristics of the recurrence and recurrence-free groups.

	Recurrence group (n=9)	Recurrence-free group (n=8)	Recurrence rate (%)	p-value
Macroscopic classification				0.127
Type 2	4	7	36.4	
Type 3	5	1	83.3	
Histologic type				0.56
tub1	3	3	50	
tub2	5	4	55.6	
pap	0	1	0	
muc	1	0	100	
Site of perforation				0.0135
Cancer site	1	4	20	
Proximal site	8	4	66.7	
T factor				0.0443
T3	4	8	50	
T4a	4	0	100	
T4b	1	0	100	
N factor				0.544
N0	5	4	55.6	
N1	3	4	42.9	
N2	1	0	100	
Stage				0.626
II	5	4	55.6	
III	4	4	50	
Adjuvant chemotherapy				
Yes	3	6	33.3	0.1442
No	6	2	75	
Number of dissected lymph nodes	5.4±4.8	12.9±7.6		0.0377

tub1: well differentiated type; tub2: moderately differentiated type pap: papillary adenocarcinoma muc: mucinous adenocarcinoma Mean±standard deviation.

iatrogenic perforation and 2 cases of fishbone perforation. In addition, in the group of patients with perforated CRC, perforation of a proximal site was more common than perforation of the cancer site in 20 cases (62.5%), which was thought to have been due to the dispersal of a large amount of stool from the proximal site, which was stenosed by the cancerous part, into the abdominal cavity.

In the cancer site perforation group, peritoneal contamination was usually localized and purulent, whereas in the proximal site perforation group it was most often diffuse and fecal. A significant difference was observed in the Hinchey stages of the two groups[9]. In the present study, the Hinchey stage of the proximal site perforation group was significantly higher in comparison to the cancer site perforation group. The reason for this, as mentioned previously, was that a perforation at a proximal site was more likely to cause a large amount of feces to spread into the abdominal cavity, due to the pressure on the intestinal tract caused by the stenosis of the cancerous area.

In the 17 patients who could be followed up (after excluding patients with stage IV disease or unknown stage), the rate of T4 disease was significantly higher than that of T3 disease in patients with postoperative recurrence. The deeper the depth, the higher the frequency of recurrence, especially in patients with T4 disease, which seemed to be an obvious result. In addition, in patients with postoperative recurrence, perforation was observed significantly more frequently at proximal sites in comparison to the cancer site. Harris et al[11] reported that in the case of cancer site perforation, because recurrence resulted from the local dissemination of cancer cells, many cases of non-hematogenous recurrence are observed at the local site, the peritoneum, and other locations. Several reports have indicated high recurrence rates both locally (15.7-44%)[9,20,21] and at distant sites (44%)[20] in patients with perforated CRC. However, the sites of recurrence and their incidence were unclear. In the present study, peritoneal recurrence or local recurrence were observed in 1 patient (50%) in the cancer site perforation group and 8 pa-

TABLE 5. Clinicopathological characteristics of the hospital mortality group and the alive at discharge group.

	Hospital mortality group (n=5)	*Alive at discharge group (n=27)*	*p-value*
Age (years)	72.4±13.8	76.3±11.6	0.516
Sex			
Male	2	17	0.620
Female	3	10	
Site of perforation			0.881
Cecum	0	2	
Ascending colon	0	1	
Transverse colon	0	3	
Descending colon	0	1	
Sigmoid colon	4	14	
Rectum	1	6	
Perforation site			0.581
Cancer site	1	11	
Proximal site	3	17	
Stage			0.576
II	1	9	
III	0	8	
IV	1	8	
Unknown	3	2	
Hinchey stage			0.0917
1	0	8	
2	0	0	
3	1	13	
4	4	6	
Operation time (min)	138±41.5	152.8±49.8	0.640
Time to operation from onset of symptoms (hours)	8±5.1	24.2±32.8	0.584
Preoperative shock			0.0169
Yes	2	0	
No	3	27	
SOFA score	2.4±2.9	1.4±1.2	0.891

Mean±standard deviation, SOFA: Sequential Organ Failure Assessment.

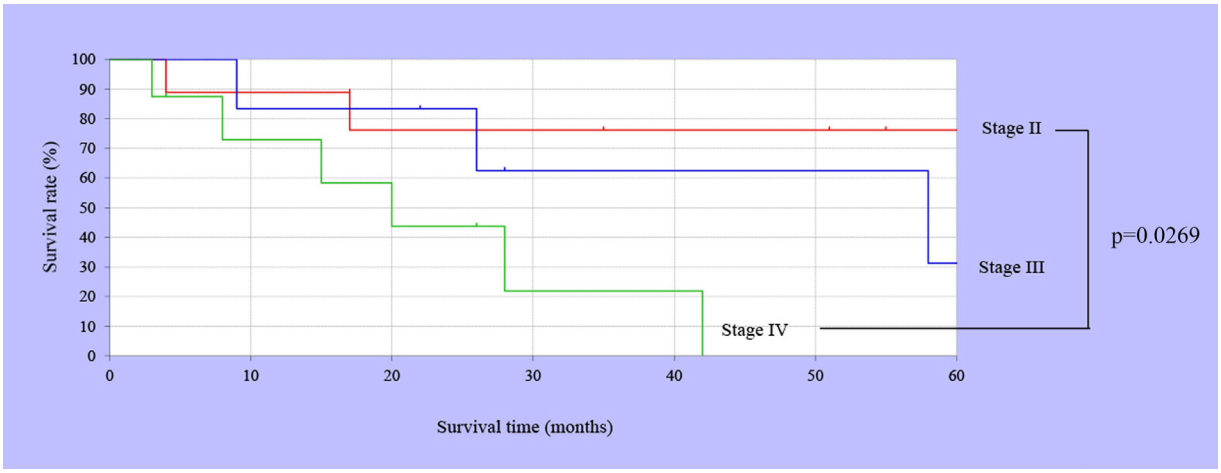

Fig. 1. Overall survival curves of patients with perforated CRC according to stage. A significant difference was observed in the 5-year overall survival rates of the stage II and IV groups (p=0.029). The 5-year overall survival rates of the stage II and stage III groups did not differ to a statistically significant extent.

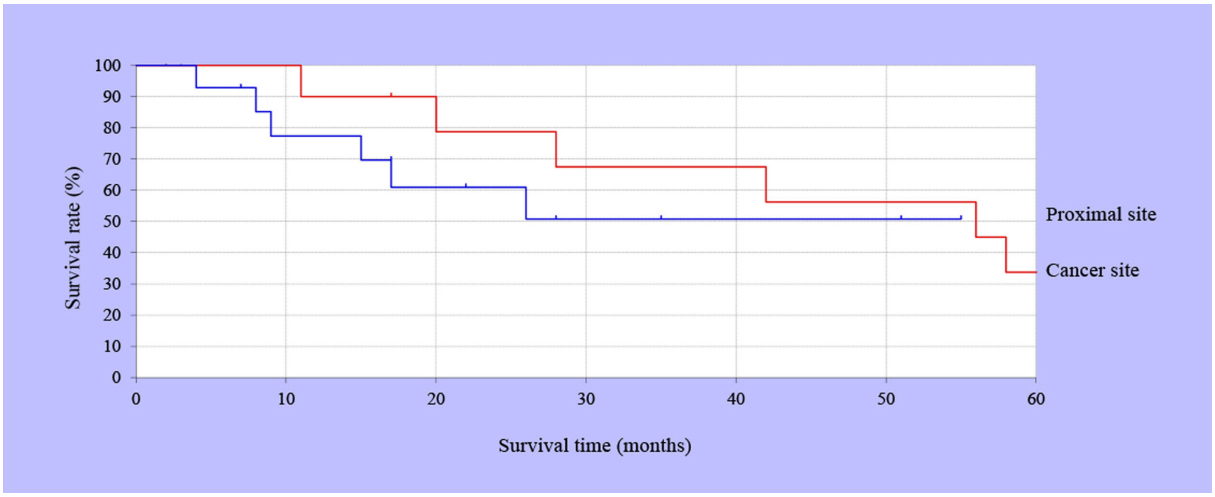

Fig. 2. Overall survival curves of patients with perforated CRC according to the site of perforation. The 5-year overall survival rates of the cancer site perforation group and proximal site perforation group did not differ to a statistically significant extent.

tients (40%) in the proximal site perforation group. The frequency of peritoneal or local recurrence at the cancer site was not lower than that at proximal sites. The reason for the more frequent recurrence in patients with proximal site perforation was that the proximal site group included more cases of liver (n=4) and lung (n=3) haematogenetic metastasis as well as peritoneal and local recurrence. Radical LN dissections cannot be performed in patients with perforated CRC, due to severe inflammation and the poor general condition of the patient. However, sufficient LN dissection (≥12 LNs) increased the overall survival of patients with perforated CRC[22]. In the present study, the number of dissected lymph nodes in the recurrence-free group was significantly higher than that in the recurrence group (p=0.0377). As the recurrence rate increases, the prognosis will naturally become worse.

In the present study, there was a tendency for more patients in the recurrence-free group to receive adjuvant chemotherapy. The recurrence rate was 33.3% in patients who received postoperative adjuvant chemotherapy, whereas it was 75% in those who did not. Although age and the patient's general condition need to be considered when determining its application, postoperative adjuvant chemotherapy was suggested to be useful for preventing postoperative recurrence in patients with perforated CRC[23,24]. Among patients with perforated CRC, the overall survival of the patients with stage II disease was not significantly different from that of patients with and stage III disease. Postoperative adjuvant chemotherapy was therefore considered necessary for patients with stage II or III disease.

The operative mortality rate in patients who receive elective surgery for CRC is 3%, whereas that for perforated (including obstructive) CRC is 2–4 times higher[25]. In the present study, the operative mortality rate was 6.3% and the hospital mortality rate was 15.6%. In patients with perforated CRC, the preoperative shock rate was significantly higher in the hospital mortality group (40%) than in the alive at discharge group (0%). Thus, preoperative shock was the only risk factor for hospital mortality in patients with perforated CRC. Radical LN dissection is recommended but cannot always be performed during surgery for perforated CRC because excessive surgical stress must be avoided when the patient is in a poor general condition[25]. In the case of perforation of CRC, if the patient is in a state of preoperative shock, surgical treatment may have to be chosen to avoid surgery-related death rather than to cure the cancer, depending on the situation.

The present study is associated with several limitations. First, the operative and postoperative management was performed by different doctors and was, therefore, inconsistent in its quality. Second, this study was conducted at a single center and the study population was relatively small. A large-scale multicenter study should be performed to confirm our findings.

CONCLUSIONS

Among patients with colorectal perforation, the Hinchey stage of the perforated CRC group was significantly higher than the non-CRC group. Furthermore, the Hinchey stage of the proximal site perforation group was significantly higher than that of the cancer site perforation group. Among the 17 patients who could be followed up (after excluding patients with stage IV disease or unknown stage), the rate of T4 disease was significantly higher than that of T3 disease in patients with postoperative

recurrence. Among patients with postoperative recurrence, perforation was observed at proximal sites significantly more frequently in comparison to cancer sites. Third the number of dissected lymph nodes in the recurrence-free group was significantly higher than that in the recurrence group. Among patients with perforated CRC, postoperative adjuvant chemotherapy was considered necessary for stage II disease as well as those with stage III disease. Preoperative shock was an independent risk factor for hospital mortality in patients with perforated CRC. In order to improve the mortality rate and prognosis of patients with perforated CRC, it is important to identify patients with risk factors for recurrence and hospital mortality, select an appropriate surgical procedure, and provide intensive treatment.

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Informed Consent:
All participants in this study signed the informed consent.

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Availability of data and materials:
All data generated or analyzed during this study are included in this published article.

Contributions:
Udaka T analyzed the data and wrote the manuscript. Udaka T, Endou I, Yoshida O, and Kubo M performed the surgery, and Asano H and Kubo M helped draft the manuscript. Nishiyama T, Watanabe N, Endou I, Yoshida H, and Kubo M participated in revising the manuscript critically. All authors declare that they contributed to this article and that they read and approved the final version.

Conflict of Interest:
All authors declare that there are no conflicts of interest.

REFERENCES

1. Alvarez JA, Baldonedo RF, Bear IG, Otero J, Pire G, Avarez P, Jorge J. Outcome and prognostic factors of morbidity and mortality in perforated sigmoid diverticulitis. Int Surg 2009; 94: 240-248.
2. Horiuchi A, Watanabe Y, Doi T, Sato K, Yukumi S, Yoshida M, Yamamoto Y, Sugishita H, Kawachi K. Evaluation of prognostic factors and scoring system in colonic perforation. World J Gastroenterol 2007; 13: 3228-3231.
3. Kriwanek S, Armbruster C, Beckerhinn P, Dittrich K. Prognositic factors for survival in colonic perforation. Int J Colorectal Dis 1994; 9: 158-162.
4. Bielecki K, Kamiński P, Klukowski M. Large bowel perforation: morbidity and mortality. Tech Coloproctol 2002; 6: 177-182.
5. Biondo S, Parés D, Martí Ragué J, De Oca J, Toral D, Borobia FG, Jaurrieta E. Emergency operations for nondiverticular perforation of the left colon. Am J Surg 2002; 183: 256-260.
6. Biondo S, Ramos E, Deiros M, Ragué JM, De Oca J, Moreno P, Farran L, Jaurrieta E. Prognostic factor for mortality in left colonic peritonitis: a new scoring system. J Am Coll Surg 2000; 191: 635-642.
7. Yamamoto T, Kita R, Masui H, Kinoshita H, Sakamoto Y, Okada K, Komori J, Miki A, Uryuhara K, Kobayashi H, Hashida H, Kaihara S, Hosotani R. Prediction of mortality in patients with colorectal perforation based on routinely available parameters: a retrospective study. World J Emerg Surg 2015: 10; 24. Doi: 10.1186/s13017-015-0020-y.
8. Khan S, Pawlak SE, Eggenberger JC, Lee CS, Szilagy EJ, Margolin DA. Acute colonic perforation associated colorectal cancer. Am Surg 2001; 67: 261-264.
9. Carraro PG, Segala M, Orlotti C, Tiberio G. Outcome of large-bowel perforation in patients with colorectal cancer. Dis Colon Rectum 1998; 41: 1421-1426.
10. Mandava N, Kumar S, Pizzi WF, Aprile IJ. Perforated colorectal carcinomas. Am J Surg 1996; 172: 236-238.
11. Harris GJ, Church JM, Senagore AJ, Lavery IC, Hull TL, Strong SA, Fazio VW. Factors affecting local recurrence of colonic adenocarcinoma. Dis Colon Rectum 2002; 45: 236-238.
12. Biondo S, Martí-Ragué J, Kreisler E, Parés D, Martín A, Navarro M, Pareja L, Jaurrieta E. A prospective study of outcomes of emergency and elective surgeries for complicated colonic cancer. Am J Surg 2005; 189: 377-383.
13. Vincent JL, de Mendonça A, Cantraine F, Moreno R, Takala J, Suter PM, Sprung CL, Colardyn F, Blecher S. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problem" of the European Society of Intensive Care Medicine. Crit Care Med 1998; 26: 1793-1800.
14. Japanese Society for Cancer of the Colon and Rectum ed). JSCCR Guideline 2021 for the treatment of colorectal cancer. Kanehara Inc, Tokyo.
15. Brierley JD, Gospodarowicz Mk, Witterkind C. TMN classification of malignant tumors (8th ed.) Wiley Blackwell, 2017.
16. Shimazaki J, Motohashi G, Nishida K, Ubukata H, Tabuchi T. Postoperative arterial blood lactate level as a mortality marker in patients with colorectal perforation. Int J Colorectal Dis 2014; 29: 51-55.
17. Irvin GL 3rd, Horsley JS 3rd, Caruana JA Jr. The morbidity and mortality of emergent operations for colorectal disease. Ann Surg 1984; 199: 598-603.
18. Shinkawa H, Yasuhara H, Naka S. Factors affecting the early mortality of patients with nontraumatic colorectal perforation. Surg Today 2003; 33: 13-17.
19. Komatsu S, Shimomatsuya T, Nakajima M, Yanagie H, Nojiri T, Furuya Y, Ariki K, Niwa H. Prognostic factors and scoring system for survival in colonic perforation. Hepatogastroenterology 2005; 52: 761-764.
20. Willett C, Tepper JE, Cohen A, Oriow E, Welch C. Obstructive and perforative colonic carcinoma: patters of failure. J Clin Oncol 1985; 3: 397-834.

21. Cheynel N, Cortet M, Lepage C, Ortega-Debalon P, Faivre J, Bouvier AM. Incidence, patterns of failure, and prognosis of perforated colorectal cancers in a well-defined population. Dis Colon Rectum 2009; 52: 406-411.
22. Sugawara K, Kawaguchi Y, Nomura Y, Koike D, Nagai M, Tanaka N. Insufficient lymph node sampling in patients with colorectal cancer perforation is associated with an averse oncological outcome. World J Surg 2017; 41: 295-305.
23. Hirose H, Miyazaki S, Fujita S, Miyazaki Y, Sugimoto S, Michiura T, Yamabe K, Nagaoka M. Clinical outcomes pf 13 patients with perforated colorectal cancer. Gan To Kagaku Ryouho 2014; 41: 1728-1730.
24. Asano H, Kojima K, Ogino N, Fukano H, Ohara Y, Shinozuka N. Postoperative recurrence and risk factors of colorectal cancer perforation. Int J Colorectal Dis 2017; 32: 419-424.
25. Alcobendas F, Jorba R, Poves I, Busquets J, Engel A, Jaurrieta E. Perforated colonic cancer. evolution and prognosis. Rev Esp Enferm Dig 2000; 92: 326-333.