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RESEARCH

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Factors associated with postoperative recurrence in perforated colorectal cancer: unraveling the high recurrence rate of perforated colorectal cancer

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Abstract

Background Perforated colorectal cancer exhibits a higher recurrence rate than non-perforated colorectal cancer; however, the reasons for this difference remain unclear. This study identifies factors affecting recurrence in patients with perforated colorectal cancer who underwent R0 surgery.

Methods This study included consecutive patients with Stage II or III perforated colorectal cancer who underwent radical surgery at a single center between 2007 and 2020. The comparison group included patients with non-perforated, non-obstructive, non-perforated colorectal cancer who underwent surgery during the same period. Clinicopathological background factors (age, sex, localization, surgical procedure, stoma, T stage, lymphatic invasion, venous invasion, differentiation, extent of lymph node dissection, number of dissected lymph nodes, lymph node metastasis, postoperative complications, and 30-day postoperative death) of perforated and non-perforated colorectal cancers were investigated. Factors influencing recurrence were examined in patients who were followed for more than 3 years after surgery, up to 5 years postoperatively.

Results This study included 89 perforated and 323 non-perforated cases. The median patient ages were 74 and 73 years in the perforated and non-perforated groups, respectively. In perforated cases, the proportion of T4 stage tumors was significantly higher (39% vs. 18% in non-perforated cases, with $p < 0.001$). Additionally, the number of lymph node dissections was significantly lower (10 vs. 17 in non-perforated cases, $p < 0.001$), and the rate of postoperative complications was higher (46% vs. 7% in the non-perforated cases, $p < 0.001$). Postoperatively, 55 perforated and 284 non-perforated cases were available for follow-up. Univariate analysis revealed that perforation, T4 stage, lymph node metastases, and postoperative complications were associated with significantly higher recurrence rates. Multivariate analysis identified T4 stage and lymph node metastases as independent risk factors.

Conclusions The recurrence rate of perforated colorectal cancer was higher than that of non-perforated cases, primarily due to advanced disease stages, such as T4 or lymph node metastases. Perforation itself may not directly cause recurrence but reflects cancer progression. Further research is needed to clarify the mechanisms linking cancer progression, perforation, and recurrence.

Keywords Intestinal perforation, Colorectal neoplasms, Neoplasm staging

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Background

Colorectal perforation can easily lead to sepsis, disseminated intravascular coagulation (DIC), and multiple organ failure, with a mortality rate of 12–26% [1–5]. While perforation has various causes, including cancer, diverticulum, and idiopathic disease, over half of the cases are benign, and long-term survival is likely if the acute stage is managed. However, because colorectal cancer perforation is a malignant disease, the risk of cancer recurrence must be considered in the long term, even after the acute stage is stabilized.

In addition to lymphatic and venous invasion, as well as pT4 staging, clinical factors such as bowel obstruction and perforation are considered risk factors for colorectal cancer recurrence [6, 7]. Perforated colorectal cancer exhibits a higher recurrence rate than non-perforated colorectal cancer [8–12]. This increased recurrence is likely attributed to reduced dissection owing to life-saving priorities [13, 14] and the dissemination of cancer cells associated with perforation [15, 16]. While some reports indicate that distant recurrence is common, as with non-perforated colorectal cancer [9, 13], others suggest that local recurrence is more prevalent in perforated cases [15]. We have previously investigated the mechanisms underlying recurrence in Stages II and III perforated colorectal cancer and found no significant differences in the extent of colorectal resection or recurrence patterns. However, in all stages, T4 cases were significantly more common in perforating colorectal cancer [17, 18]. Although T4 alone cannot determine the overall stage, T4 is considered a factor affecting the recurrence of colorectal cancer [19, 20]; thus, we hypothesized that this advanced stage would be more prone to perforation and would involve a higher recurrence rate.

Therefore, in the present study, we aimed to identify factors associated with postoperative recurrence in perforated colorectal cancer, comparing outcomes to non-perforated colorectal cancer treated concurrently at a single institution.

Methods

Patient enrollment

A retrospective observational study was conducted on patients with colorectal cancer who underwent surgery at the Saitama Medical University Department of General Surgery between 2007 and 2020.

Perforated and non-perforated cases were selected from pathological R0 colorectal cancer cases, excluding Stage 0, I, or IV cases. Perforation was determined based on intraoperative findings, the presence of intra-abdominal free gas, and peri-intestinal abscess formation observed in preoperative abdominopelvic computed tomography (CT) scans. Perforation cases included emergency surgery, those treated with percutaneous drainage or antimicrobial agents before surgery, and those managed with elective surgery. Patients with iatrogenic perforations, such as those caused by stent placement, were excluded. Cases of intraoperative perforation and leakage of intestinal contents without preoperative evidence of perforation were classified as non-perforated cases. Additionally, patients with a history of preoperative bowel obstruction or those who had undergone decompression procedures, such as stenting or colostomy, for obstructed passage were excluded from the non-perforation group.

Perforation types were classified as tumor site perforation, where the perforated area coincided with the carcinoma, and proximal perforation, where normal mucosa was present between the perforated area and the tumor.

Surgical technique

In all cases, surgery for colorectal perforation was performed via laparotomy. For left-sided colon perforation, a Hartmann procedure is typically performed, in which the tumor and perforated area are resected and a colostomy is created on the oral side. However, for right-sided colon perforation, a primary anastomosis is performed. If the time from onset is short and the contamination of the abdominal cavity is mild, a primary anastomosis could also be performed on the left-sided perforation. Resection and anastomosis of the intestinal tract are performed using an automatic suture or an automatic anastomosis device.

The peritoneum was washed with ≥ 10,000 mL of saline solution, and a closed drain was implanted in the pelvic floor. To close the abdomen, the muscle layer was closed with interrupted monofilament absorbable sutures, and the skin was closed with subcutaneous monofilament absorbable sutures after washing the subcutaneous tissue with 1,000 mL of saline solution. Carbapenem was administered before surgery.

Clinicopathological background

Data on age, sex, tumor localization, surgical procedure, T stage, lymphatic invasion, venous invasion, histological type, extent of lymph node dissection, number of lymph nodes dissected, lymph node metastasis, postoperative complications, and 30-day postoperative death were obtained from medical records. The clinicopathological characteristics of perforated and non-perforated cases were compared. The Union for International Cancer Control (UICC) TNM system was used for cancer stage classification [21].

R0 was defined as the absence of residual cancer on intraoperative examination and pathologically negative dissected margins or surfaces. For the tumor localization,

the cecum, ascending colon, and transverse colon were defined as the right-sided colon; and the descending colon, sigmoid colon, and rectum were defined as the left-sided colon. Surgical procedures were classified as laparoscopic surgery and open surgery and cases requiring conversion were classified as open surgery cases. The presence of a stoma was also examined. Regarding the extent of lymph node dissection, standard lymph node dissection involved the main lymph nodes; otherwise, the operation was considered reduced lymph node dissection.

Follow-up

Patients with lymph node metastasis, perforation, T4 stage, poorly differentiated adenocarcinoma, venous invasion, lymphatic invasion, or lymph node dissection of less than 12 nodes were considered at high risk for recurrence and were administered adjuvant chemotherapy upon request. The adjuvant chemotherapy regimen included oral tegafur/uracil/oral leucovorin (500 mg/day tegafur/uracil +75 mg/day oral leucovorin, administered over four weeks with one week of rest), oral capecitabine (1000 mg/m^2 twice daily for two weeks in a three-week cycle), or oral capecitabine plus intravenous oxaliplatin (130 mg/m^3 on Day 1 in a three-week cycle) for six months. Initially, the oral tegafur/uracil/oral leucovorin was selected; however, in 2011, it was changed to a capecitabine-based regimen. There were no strict criteria for using oxaliplatin in combination. However, if the patient wished to use it, it was administered with the drug after explaining the complications, such as peripheral neuropathy and renal dysfunction. If the patient could not continue the treatment because of adverse events, it was considered as no adjuvant therapy. After surgery, carcinoembryonic antigen and cancer antigen 19–9 were measured every 6 months for 5 years, and CT scans of the thorax, abdomen, and pelvis were performed. Lower gastrointestinal endoscopy was performed annually. Recurrence was determined using imaging findings, such as CT and lower gastrointestinal endoscopy; histological diagnosis was not required. The date of recurrence was defined as the date of the examination. Local recurrence was defined as lesions that appeared in the peritoneum or soft tissue adjacent to the anastomotic site or original tumor site, whereas peritoneal recurrence referred to disseminated lesions that occurred distant from the original tumor site.

Risk factors for recurrence

Factors contributing to recurrence were analyzed, excluding cases involving in-hospital deaths. The study included patients who were discharged and subsequently followed up for death or recurrence or who were followed up for more than 36 months. Univariate analysis was performed to assess the recurrence rate based on localization, surgical procedure, stoma, T stage, lymphatic invasion, venous invasion, extent of lymph node dissection, number of lymph nodes, lymph node metastasis, postoperative complications, postoperative adjuvant chemotherapy, and perforation. Additionally, multivariate analysis was performed for factors that were statistically significant in the univariate analysis.

Recurrence form

Organs affected by recurrence were compared between the perforated and non-perforated groups. In patients with perforated colorectal cancer, these organs were also compared according to the perforation type.

Statistical analysis

All statistical analyses were performed using the Bell Curve for Excel (Social Survey Research Information Co.). Categorical variables, such as sex, tumor localization, T stage, lymphatic invasion, venous invasion, histologic type, and recurrence, were expressed as numbers and percentages, whereas quantitative variables, including age and number of dissected lymph nodes, were presented as medians (interquartile range). The chi-square test was used to analyze categorical variables. The Mann–Whitney U test was utilized to analyze continuous quantitative variables, including age and the number of lymph nodes dissected. Univariate analysis was conducted using the chi-square and Mann–Whitney U tests. Multivariate analysis was performed using logistic regression analysis to identify independent risk factors for recurrence. The 95% confidence interval indicates the range where the true odds ratio is expected to lie with 95% confidence. This non-parametric test was employed owing to the non-normal distribution of the variables. Survival curves for the postoperative recurrence-free period were evaluated using the Kaplan–Meier method, and statistical differences were analyzed utilizing the log-rank test. Regarding the analysis of the recurrence-free period, events were defined as recurrences. Statistical significance was set at $p < 0.05$.

Results

Between 2007 and 2020, 874 colorectal cancer surgeries were performed. Of these, 569 patients were diagnosed with Stage II or III disease following R0 surgery. Patients with bowel obstruction due to a tumor or medically induced perforation from preoperative endoscopic stenting were excluded. Preoperative abdominal and pelvic CT scans identified free gas or abscess formation in 89 patients, who were classified as the perforated group. The remaining 323 patients, who underwent elective surgery

without perforation or bowel obstruction, were classified as the non-perforated group.

The number of patients who were followed up after surgery was 55 and 284 in the perforated and non-perforated groups, respectively (Fig. 1).

Clinicopathological patient background

The median age was 74 and 73 years in the perforated and non-perforated groups, respectively. Tumors accounted for 80% and 54% of the perforated and non-perforated groups, respectively, with a higher percentage of left-sided colon cancers in the perforated group. All perforation cases were treated with open surgery. In the case of patients who had a stoma constructed, there were 23 cases (7%) of non-perforation. The surgical procedure was abdominoperineal rectal resection in 13 cases, total pelvic exenteration in 2 cases, and other in 36 cases. In the case of perforation, a stoma was constructed in 51 cases (57%), and the tumor including the perforated part was resected in all cases, and a colostomy was performed using the intestinal tract on the oral side. The percentage of T4 cases was significantly higher in the perforated group (39%) than in the non-perforated group (18%). There were no significant differences in lymphatic or venous invasion or differentiation between the two groups. The extent of lymph node dissection was reduced in the perforated group, and the number of dissected lymph nodes was significantly higher in the non-perforated group (17 nodes) than in the perforated group (10 nodes). Postoperative complication (46% vs. 7%, $p < 0.001$) and mortality rates (8% vs. 0.3%, $p < 0.001$) were significantly higher in the perforated group (Table 1).

Risk factors for recurrence

Univariate analysis of recurrence factors was performed in 55 patients from the perforated group and 284 patients from the non-perforated group, who were available for follow-up. Univariate analysis revealed that the recurrence rates were significantly high for open surgery (31% vs. 18%, $p = 0.15$), stoma (43% vs. 23%, $p = 0.001$), T4 (44% vs. 22%, $p < 0.001$), lymph node metastases (35% vs. 21%, $p = 0.0056$), postoperative complications (39% vs. 22%, $p = 0.013$), and perforation (44% vs. 24%, $p = 0.0021$). Multivariate analysis identified the T4 stage (95% CI 1.33–4.26 $p = 0.0033$) and lymph node metastasis (95% CI 1.18–3.27 $p = 0.0092$) as independent risk factors (Table 2).

Long-term outcomes

The median follow-up period for all patients was 28 months (interquartile range [IQR]: 6–58 months). Recurrence was confirmed in 44% and 24% in the perforated and non-perforated groups, respectively. The recurrence-free rates at 1 and 5 years were 75% and 49%, respectively, in the perforated group. In the non-perforated group, the recurrence-free rates were 89% and 70% at 1 and 5 years, respectively (Fig. 2).

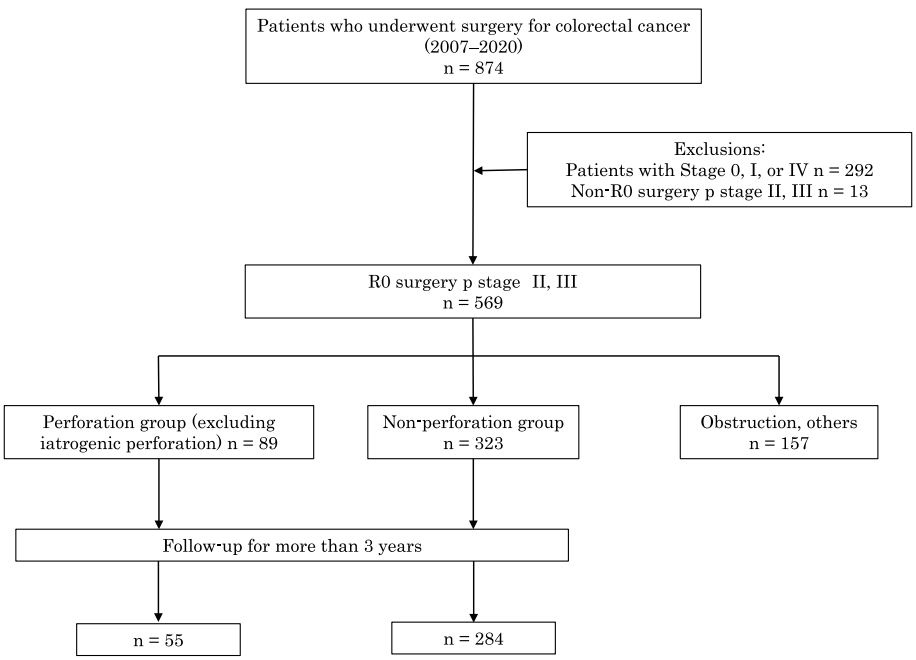

Fig. 1 Flowchart showing the selection of the study population

Table 1 Clinicopathological characteristics of patients

		Perforation $n = 89$	No perforation $n = 323$	*P*-value
Age, years		74 (67–84)	73 (68–79)	0.098
Sex	Male	53 (60%)	191 (59%)	0.943
	Female	36 (40%)	132 (41%)	
Localization	Left sided	72 (80%)	175 (54%)	< 0.001
	Right sided	17 (20%)	148 (46%)	
Surgical procedure	Open	89 (100%)	209 (65%)	< 0.001
	Laparoscopic	0 (0%)	114 (35%)	
Stoma	Yes	51 (57%)	23 (7%)	< 0.001
	No	38 (43%)	300 (93%)	
Pathological T stage	T1–T3	54 (61%)	265 (82%)	< 0.001
	T4	35 (39%)	58 (18%)	
Lymphatic invasion	No	43 (48%)	196 (61%)	0.36
	Yes	46 (52%)	127 (39%)	
Venous invasion	No	30 (34%)	120 (37%)	0.21
	Yes	69 (66%)	203 (63%)	
Differentiation grade	Well, moderate	81 (91%)	275 (85%)	0.15
	others	8 (9%)	48 (15%)	
Extent of lymph node dissection	Standard D3	17 (19%)	206 (64%)	< 0.001
	Reduced D0–2	72 (81%)	117 (36%)	
Number of dissected lymph nodes		10 (4–13)	17 (10–23)	< 0.001
Lymph node metastasis	Yes	36 (40%)	134 (41%)	0.86
	No	53 (60%)	189 (59%)	
Clavien–Dindo	0–I	26 (29%)	252 (78%)	< 0.001
	II–V	663 (71%)	71 (22%)	
30-day postoperative death		7 (8%)	1 (0.3%)	< 0.001

Form of recurrence

Recurrence occurred in 24 patients (44%) in the perforated group; distant recurrence occurred in 15 patients (63%); and local recurrence occurred in 8 patients (33%). In contrast, in the non-perforated group, 67 (24%) patients had recurrence, 43 (64%) had distant recurrence, and 17 (25%) had local recurrence, with no difference in recurrence type or organ type between the perforated and non-perforated groups (Table 3).

In the perforated group, 21 patients had perforations at the tumor site, and 34 patients had perforations at the proximal site. There was no difference in the recurrence rate between perforation at the tumor and proximal sites. However, the recurrence rate of distant recurrence was significantly higher for perforation at the proximal site. Specifically, it was 30% in 3 cases for perforation at the tumor site and 86% in 12 cases for perforation at the proximal site. Peritoneal recurrence was significantly high in cases of perforation at the tumor site, with 3 cases (30%) with perforation at the tumor site and 0 cases (0%) with perforation at the proximal peritoneal site (Table 4).

Discussion

The recurrence rate of perforated colorectal cancer is reportedly higher than that of non-perforated colorectal cancer [10–14]. This study confirms these findings, demonstrating a 44% recurrence rate for perforated colorectal cancer compared with a 24% recurrence rate for non-perforated colorectal cancer. Potential reasons for this phenomenon include the dispersal of cancer cells following perforation [17, 18] and the prioritization of life-saving measures over additional surgeries [22–24]. Additionally, peritonitis following perforation may contribute to increased recurrence rates [25, 26]. This occurs because suture failure post-colon cancer surgery promotes the adhesion of cancer cells due to peritoneal inflammation, increasing the risk of recurrence [27–29]. If perforation is a factor in recurrence, then local or peritoneal recurrence due to the dissemination of cancer cells into the peritoneal cavity is more likely. However, our previous studies on perforated colorectal cancer found no significant difference in recurrence patterns or extent of colon cleansing compared with non-perforated colorectal cancer [19, 20]. Given that T4 cases are significantly pronounced in

Table 2 Univariate and multivariate analyses of factors associated with recurrence

				Univariate	Multivariate	
			Recurrence	***P*-value**	**95% CI**	***P*-value**
Localization	Left sided	208	63 (30%)	0.07		
	Right sided	131	28 (21%)			
Surgical procedure	Open	234	72 (31%)	0.015	0.75–2.63	0.29
	Laparoscopic	105	19 (18%)			
Stoma	Yes	65	28 (43%)	0.0010	0.71–3.67	0.25
	No	274	63 (23%)			
Pathological T stage	T1–T3	267	59 (22%)	< 0.001	1.33–4.26	0.0033
	T4	72	32 (44%)			
Lymphatic invasion	No	205	50 (24%)	0.21		
	Yes	134	41 (31%)			
Venous invasion	No	122	30 (25%)	0.48		
	Yes	217	61 (28%)			
Extent of lymph node dissection	Standard D3	204	51 (25%)	0.35		
	Reduced D0–2	135	40 (30%)			
Number of dissected lymph nodes	≥ 12	216	57 (26%)	0.80		
	< 12	123	34 (28%)			
Lymph node metastasis	No	198	42 (21%)	0.0056	1.18–3.27	0.0092
	Yes	141	49 (35%)			
Clavien–Dindo	0–I	245	54 (22%)	0.0013	0.93–3.01	0.088
	II–V	94	37 (39%)			
Adjuvant chemotherapy	With	110	29 (26%)	0.89		
	Without	229	62 (27%)			
Perforation	Absence	284	67 (24%)	0.0021	0.45–2.49	0.90
	Presence	55	24 (44%)			

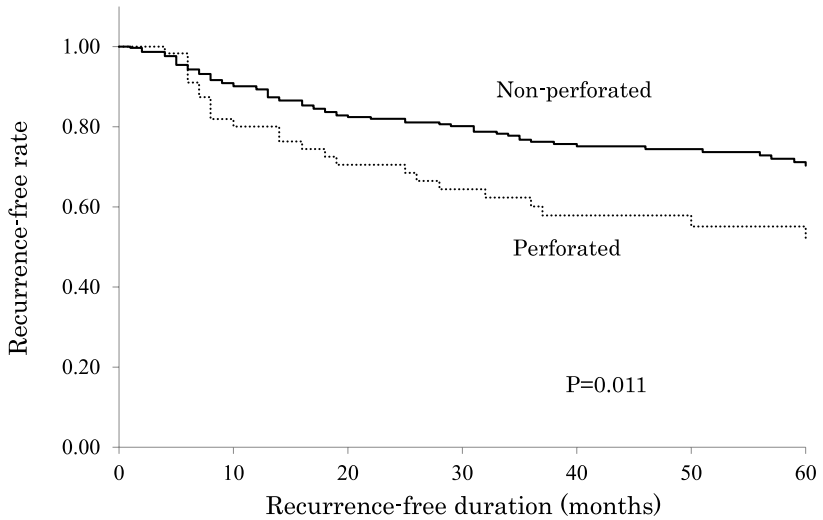

Fig. 2 Recurrence-free curves for the perforated and non-perforated groups of patients who underwent postoperative follow-up

Table 3 Recurrence patterns with or without perforation

	Perforation $n = 55$	Non-perforation $n = 284$	*P*-value
Recurrence	24 (44%)	67 (24%)	
Location of recurrence			
Distant	15 (63%)	43 (64%)	0.8
Local	8 (33%)	17 (25%)	0.45
Peritoneum	3 (13%)	6 (9%)	0.62
Lymph node	2 (8%)	4 (6%)	0.69

A duplication exists in the site of recurrence

Table 4 Recurrence patterns of site of perforation

	Tumor site $n = 21$	Proximal site $n = 34$	*P*-value
Recurrence	10 (48%)	14 (41%)	0.64
Location of recurrence			
Distant	3 (30%)	12 (86%)	0.0054
Local	4 (40%)	4 (29%)	0.56
Peritoneum	3 (30%)	0 (0%)	0.029
Lymph node	1 (10%)	1 (7%)	0.80

A duplication exists in the site of recurrence

perforated colorectal cancer, we hypothesized that the recurrence rate is not directly increased by perforation but rather reflects the advanced stage of cancer, leading to both perforation and a higher recurrence rate. In this study, univariate analysis of the clinicopathological background of patients in the perforated and non-perforated groups identified open surgery, T4 stage, lymph node metastasis, postoperative complications, and perforation as recurrence factors, whereas multivariate analysis identified T4 stage and lymph node metastasis as independent risk factors. These results suggest that recurrence is not directly caused by perforation but rather that perforation occurs owing to cancer progression, resulting in a high recurrence rate.

In addition, we observed no difference in recurrence patterns between the perforated and non-perforated groups, and distant metastasis was common, as typically observed in colorectal cancer. There was no difference in recurrence rates according to the type of perforation; however, distant recurrence was significantly more common in patients with proximal site perforation, and peritoneal recurrence was significantly more common in patients with perforation at the tumor site. Although proximal site perforation and tumor site perforation are both types of colorectal cancer perforation, they differ significantly in their mechanisms. Proximal site perforation typically occurs in the normal mucosa, a non-cancerous tissue, owing to increased intestinal pressure. In contrast, perforation of the tumor site typically progresses to tumor self-destruction, eventually leading to perforation of the peritoneal cavity. Therefore, compared to the proximal perforation site, perforation of the cancerous area is considered a gradual process of self-destruction rather than a sudden onset. Moreover, the tumor is more likely to be covered by the surrounding tissue, which may result in a longer time lapse between the perforation and surgery. Therefore, the surrounding tissues are more likely exposed to cancerous tissues, increasing the likelihood of local or peritoneal recurrence. Half of the patients with perforated colorectal cancer experience recurrence within 1 year of surgery. This is likely owing to the potential metastasis of cancer cells potentially to distant organs, which may not be evident at the time of surgery. Given that the disease-free interval (DFI) of colorectal cancer tends to shorten as the cancer progresses [30] and that patients with a short DFI have a poor prognosis [31], it has been suggested that perforated colorectal cancer represents a state in which the cancer has already progressed.

This study is limited by the small number of cases. There were 89 cases of perforated colorectal cancer and 55 cases that could be followed up for more than 3 years. This small sample size may affect the statistical power and generalizability of the results. Generally, patients with postoperative colorectal cancer are followed up for 5 years to check for recurrence. However, follow-up was not feasible in some cases owing to patient autonomy or preference against follow-up appointments. Therefore, 39 patients with non-perforated colorectal cancer and 34 with perforated colorectal cancer were lost to follow-up. In cases of perforated colorectal cancer, patients' activities of daily living decline significantly during hospitalization, often requiring admission to a facility, which makes imaging tests, consultations, and follow-up challenging or impossible in many cases. The rarity of perforated colorectal cancer limits the sample size. Thus, accumulating cases and conducting further research using large-scale data sets is crucial to clarify the factors causing recurrence.

Conclusions

The recurrence rate of perforated colorectal cancer is higher than that of non-perforated colorectal cancer, primarily because of its association with advanced stages of the disease, such as T4 and lymph node metastases. This study suggests that perforation does not directly cause recurrence; rather, the advanced stage of cancer contributes to both perforation and a higher recurrence rate. Future research should elucidate the detailed mechanisms linking cancer progression and perforation and their impact on recurrence.

Abbreviations

ADLs	Activities of daily living
CT	Computed tomography
DIC	Disseminated intravascular coagulation
DFI	Disease-free interval

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Authors' contributions
T.M and A.H wrote the main manuscript text and prepared figures 1-2. All authors reviewed the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
All procedures involving human participants performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the Institutional Review Board of Saitama Medical University Hospital (No. 19071), which waived the requirement for written informed consent from the participants owing to its retrospective design.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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