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Do Types of Perforation Impact Outcomes in Perforated Stage II/III Colorectal Cancer Patients?

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The purpose of this paper is to compare the oncologic outcomes between colorectal cancer (CRC) patients with tumor perforation and those with perforation proximal to the tumor. Medical charts of 39 patients who underwent emergency surgery for colonic perforation related to potentially curable CRC were reviewed. Eighteen patients developed tumor perforation (group A), whereas 21 patients developed perforation proximal to the tumor (group B). Twenty-four patients were pathologic stage II and 15 patients were stage III. There were no significant differences in the clinicopathologic and surgical data, including hospital mortality, between the groups; however, the incidence of diffuse peritonitis was higher in group B than that in group A ($P < 0.01$). The induction rates of adjuvant chemotherapy for survivors were identical between the 2 groups. Disease-free and overall survival periods did not significantly differ between the groups. Perforation type was not found to be associated with oncologic outcomes in patients with CRC-related perforation.

Key words: Colorectal cancer – Perforation

Perforation occurs between 2.6% and 10% in patients with colorectal cancer (CRC).[1–4] Patients with perforated CRC have been reported to have worse prognosis than those with nonperforated CRC.[5,6] Clinically, perforated CRC is classified as with tumor perforation when perforation occurs at the site of the tumor and as noncancer perforation when perforation occurs secondary to cancer obstruction. Little is known about the potential differences in clinical outcomes between tumor

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perforation and noncancer perforation. The aim of this retrospective study was to determine whether the type of perforation was associated with oncologic outcomes in patients with perforated CRC.

Patients and Methods

Patients

Medical charts of 39 patients who underwent emergency surgery for colonic perforation related to potentially curable CRC at the Saitama Medical Center between April 1998 and March 2012 were reviewed. The patients were assigned to the following 2 groups: tumor perforation group (group A) and noncancer perforation group (group B). All patients in group B had perforation proximal to the tumor. There were 22 males and 17 females, with a median age of 67 years (range: 28–88 years). Group A included 18 patients, whereas group B included 21 patients. Twenty-four patients were pathologic stage II, and 15 patients were stage III. We performed CRC staging based on the 7th edition of the Union for International Cancer Control TNM staging system for colorectal carcinoma.[7]

Evaluation of clinical outcome

We retrospectively analyzed clinicopathologic characteristics, surgical data, patterns of recurrence, disease-free survival (DFS), and overall survival (OS) of these patients.

The first site of recurrence was recorded. The pattern of recurrence was classified as hematogenous metastasis (liver, lung, and bone) or local/peritoneal recurrence.

Statistical Analysis

The Mann–Whitney *U* test or Student's *t* test was used to compare continuous variables between the 2 groups. Categoric variables were compared using the chi-square test or Fisher's exact test as appropriate. The DFS and OS rates were analyzed using the Kaplan–Meier method, and the log-rank test was used to assess statistical significance. Survival time was calculated from the date of resection to the date of death, recurrence, or latest follow-up. All statistical calculations were performed using the JMP version 5.0 software (SAS Institute Inc., Cary, NC, USA). Differences were considered to be significant for P values <0.05.

Results

A comparison of the characteristics of the 39 patients who underwent emergency surgery for colonic perforation is presented in Table 1. The incidence of diffuse peritonitis was higher in group B (90.5%) than in group A (50%; $P < 0.01$). Furthermore, the number of patients who underwent stoma construction was larger in group B than in group A ($P = 0.01$). There were no significant differences in age, sex, location of perforation, and pathologic stage between the 2 groups. There was no significant difference in hospital mortality between the groups (6% versus 14%, respectively; $P = 0.36$).

There was no significant difference in the induction rates of postoperative adjuvant chemotherapy in the survivors between the 2 groups (65% versus 61%, $P = 0.83$; Table 2). Specifically, 3 patients (2 in stage II and 1 in stage III) in group A and 2 patients (1 in stage II and 1 in stage III) in group B received oxaliplatin-based chemotherapy.

There was no significant difference in the cumulative recurrence rates between the groups (39% versus 29%, $P = 0.63$; Table 3). There was also no significant difference in the types of recurrence (hematogenous or local/peritoneal recurrence) between the groups. No significant differences were observed in the DFS ($P = 0.83$) and OS periods ($P = 0.71$) between the 2 groups (Fig. 1A and B).

Discussion

We found that the type of perforation was not associated with oncologic outcomes in patients with CRC-related perforation. To the best of our knowledge, this is the first retrospective study to analyze the difference in outcomes between perforation types in stage II and III CRC patients with perforation.

A previous report suggested that perforated CRC has poor prognosis, particularly for patients with stage III CRC.[8] Steinberg *et al*[9] found that neoplastic perforation was the only significant indicator for DFS. However, the effect of the type of perforation on oncologic outcomes in perforated CRC has not commonly been discussed in the literature. In recent studies,[10–12] higher perioperative mortality was associated with perforation proximal to the tumor than with tumor perforation; however, the association between perforation type and long-term survival remains controversial. Sadaf *et al*[11] reported that perforation proximal to the tumor was associ-

Table 1 Comparison of the characteristics of 39 patients who underwent emergency surgery for colonic perforation

	Group A, n = 18	Group B, n = 21	*P* value
Age	66.5 (48–86)	67 (28–88)	0.31
Sex			0.45
Female	9	8	
Male	9	13	
Perforated location			0.33
Right colon	6	3	
Left colon	9	12	
Rectum	3	6	
Distance from cancer to perforated site		5.5 (0–15.3) cm	
Operation procedure			0.01
Colectomy + primary anastomosis	9	2	
Colectomy + colostomy or ileostomy with/without tumor resection	9	18	
Colostomy only	0	1	
Hinchey stage			<0.01
I, II	9	2	
III, IV	9 (50%)	19 (90.5%)	
Pathologic stage (surgery related death)[a]			0.54
II	12	12	
III	6	9	
Surgery related death	1 (6%)	3 (14%)	0.36

[a]TNM classification (UICC 7th edition).

ated with worse long-term survival than that for tumor perforation, and Paolo *et al*[10] reported that perforation proximal to the tumor was associated with better cancer-related survival than that associated with tumor perforation. Others have reported that both types of perforation had similar prognoses.[2,13] In the present study, even though the number of cases was as small as previous studies, we demonstrated that the frequency of severe peritonitis was higher in group B, which is consistent with the result of Paolo *et al*,[10] and the 5-year DFS and OS periods did not significantly differ between the 2 groups. Because the stools that tended to be more liquid or loose in the oral colon leaked into the peritoneal cavity in oral perforation,[10] Hinchey's stage was greater in group B than in group A. Therefore, more patients underwent stoma construction surgery in group B than in group A. Consequently, it seems that oral perforation is associated with higher operative mortality. However, in this study, perioperative mortality was similar between the 2 groups.

Furthermore, we showed that the pattern of recurrence and induction rate of adjuvant chemotherapy did not differ between the 2 groups. With regard to the pattern of recurrence, some reports have stated that tumor perforation was associated with highly local and peritoneal recurrence similar to hematogenous recurrence,[10,14,15] whereas the pattern of recurrence in oral perforation has been infrequently reported. In the present study, the rate of recurrence was 39% (7/17) in group A and 29% (6/18) in group B. Moreover, hematogenous recurrence was the main recurrence pattern in both groups and was more frequent than was local recurrence. In perforated CRC, peritoneal seeding is significantly more frequent than in nonperforated CRC, possibly because of the viability of the

Table 2 Comparison of postoperative adjuvant chemotherapy in survivors

	Group A, n = 17	Group B, n = 18	*P* value
Received	11 (65%)	11 (61%)	0.83
5-FU-based chemotherapy (5-FU/LV or UFT/LV)	8	9	
oxaliplatin-based chemotherapy (FOLFOX or CapeOX)	3	2	

Table 3 Pattern of recurrence in survivors

	Group A, n = 17	Group B, n = 18	*P* value
Recurrence	7 (39%)	6 (29%)	0.63
Hematogenous metastasis	5 (71%)	4 (67%)	0.85
Liver	0	1	
Lung	4	2	
Bone	0	1	
Local recurrence/Peritoneal metastasis	2 (29%)	2 (33%)	
Local	0	1	
Peritoneal	2	1	

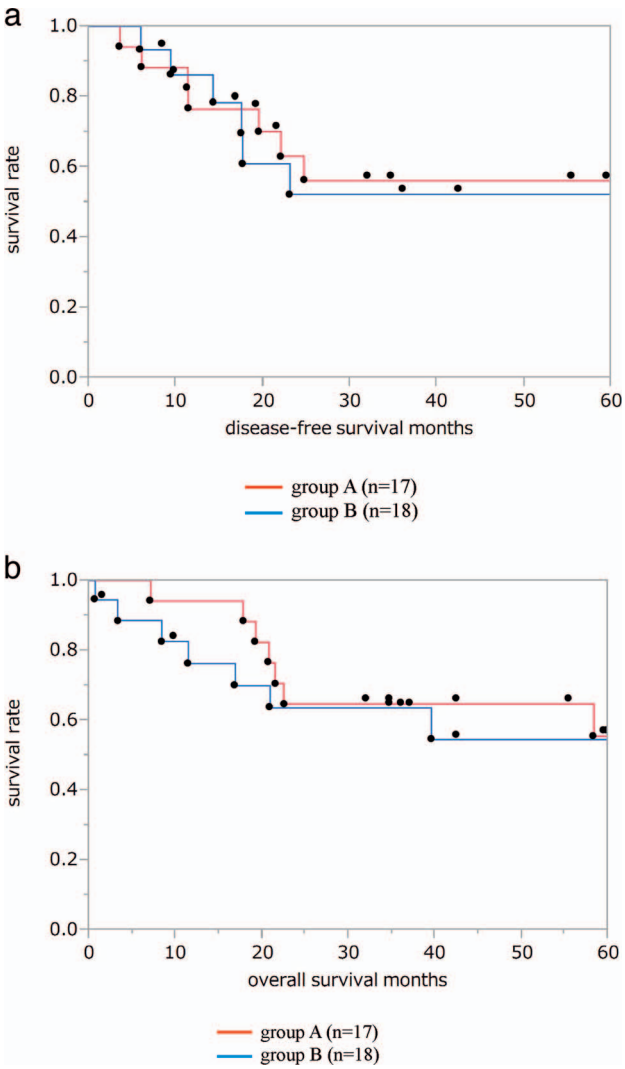

Fig. 1 Cumulative DFS and OS of the 35 patients with perforated stage II/III colorectal cancer. (A) The cumulative DFS of the 17 patients in group A was comparable with that of the 18 patients in group B ($P = 0.83$). (B) The cumulative OS of the 17 patients in group A was comparable with that of the 18 patients in group B ($P = 0.71$).

exfoliated cells.[16,17] However, recent studies have shown that neoplastic cells spreading from a perforating carcinoma may not be capable of implanting themselves in the peritoneum,[2] and the metastatic efficacy of cancer cells that are possibly shed during perforation is uncertain in the presence of peritonitis.[18]

As mentioned previously, it remains unknown whether the type of perforation has an impact on oncologic outcomes in perforated CRC. In our series, we did not perform prognostic examination between stages because of the small study sample size. Consequently, the OS rates of groups A and B were 55% and 54%, respectively, which were not significantly different. However, the OS rates of the 2 groups were worse than that of Stage IIIb CRC according to the Japanese General Rules 8th edition,[19] a finding that was consistent with previous reports[5,6] stating that long-term survival was worse for patients with perforated CRC than for CRC patients treated by elective surgery.

Although the induction rates of adjuvant chemotherapy were 65% and 61% for the 2 groups (no significant difference), effective postoperative chemotherapy appears to be required for perforated stage II and III CRC patients with a high risk of recurrence. However, the appropriate regimen for perforated stage II and III CRC patients would be controversial. In the patients who received oxaliplatin-based chemotherapy, recurrence was observed in 3 patients in group A and in 2 patients in group B, and the patients in both groups were stage II. Therefore, the difference in the effect of oxaliplatin-based chemotherapy was not clear.

There were some limitations in this study. The number of patients with perforated CRC we analyzed was small. Furthermore, this study was designed as a retrospective study. Our results indicated that the difference of the type of perforation would not affect oncologic outcome in terms of recurrence and survival. However, a prospective study with a larger series of cases should be required to confirm our conclusion in the future.

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