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A surgical outcome evaluation of perforated gastric cancer: The surgical approach

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Abstract
Objective: *Perforated gastric cancer (PGC) is an unfamiliar surgical status that develops in <5% of gastric cancers (GCs).It can be difficult to distinguish GC from a gastric ulcer at the time of surgery.In the present study, we assessed both the immediate surgical outcomes and prognosis of the underlying cancer in patients with PGC.*
Patients and methods: *A total of 23 patients were diagnosed with PGC from 1993 to 2022.The clinicopathological features of all patients were analyzed.*
Results: ***T****he mean age of the 23 patients (18 male, 5 female) was 68.6 (44-92)years old. Among the 23 patients, 14 (60.9%) were diagnosed withPGC preoperatively or intra-operatively. The stage was classified as follows: stage II (n= 2: 8.7%), stage III (n=8: 34.8%), and stage IV (n=13: 56.5%). The initial operations performed were distal gastrectomy in 9 (39.1%) patients, total gastrectomy in 3 (13.0%) patients, and simple closure with an omental patch in 11 (47.8%) patients. The two-stage gastrostomies were distal gastrectomy in one patient and total gastrectomy in twopatients. One-stage gastrectomywas performed in 12 (80.0%) patients, and 2-stage gastrectomy was performed in 3 (20.0%) patients. The cumulative 5-year survival rate was 62.1%. The survival rate ofthe 10 patients with curative R0 resectionsignificantly exceeded that of the 3 patients with non-curative R2 resection (p=0.0261).There was no significant difference in the survival rates between the 1- and the 2-stage gastrectomy groups(p=0.658).*
Conclusions: *The best surgical approach for PGC is the one that can increase the probability of safely achieving curative R0 resection to the greatest extent, and the surgeon's decision on whether to perform one- or two-stage gastrectomy should be made based on their perspective.*
Keywords: *gastric cancer, perforation, gastrectomy, curability*

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I. INTRODUCTION

Perforated gastric cancer (PGC) is an unfamiliar surgical status that develops in < 5% of gastric cancers (GCs) and is usually found in the advanced stage withmore severe complications than with a nonperforated status (1-5). It is difficult to diagnose PGC because its preoperative symptoms are the same as those of a perforated gastric ulcer (6,7). Furthermore, it may be difficult to distinguish a GC from gastric ulcer at the time of surgery, especially if an intra-operative frozen section or endoscopy is unavailable, except in cases with obvious metastatic tumors (8).

Abalanced surgical strategy should be selected in PGC while considering both peritonitis and the invasiveness of the malignancy. Historically, emergent one-stage gastrostomy was generally performed for gastric perforation with diffuse peritonitis, regardless of whether the disease was benign or malignant. One-stage gastrectomy, however, was found to be associated with high mortality rates (0%-50%) (9). Furthermore, sufficient lymph node dissection is difficult to achieve during emergent surgery for PGC, which may impair the long-term survival due to recurrence.

The introduction of two-stage gastrectomy, which includes immediate treatment of acute peritonitis with closure of the perforation site followed by curative gastrectomy with adequate lymphadenectomy, has proven to improve oncological outcomes over conventional one-stage gastrectomy (2, 3, 10, 11). The diagnosis and evaluation for the cancer status is possible during the interval with the two-stage procedure. If the perforation is caused by cancer, however, the risk of secondary leakage due to perforation cannot be excluded (12). Therefore, the standard surgical treatment for PGC has not yet been established, and the surgical approach is decided on a patient-by-patient basis, depending on the extensiveness of the gastric malignancy and degree of peritonitis.

In the present study, we assessed both the immediate surgical outcomes and prognosis of the underlying cancer in patients who presented with PGC to evaluate the clinical results of treatment and propose a practical treatment strategy.

II. Patients and methods

Patients

In this retrospective cohort study of PGC, we evaluated all 1,928 patients who underwent surgical resection for GC at Mitoyo General Hospital from January 1993 to December2022. Among the 1,928 patients, 23 (1.2%)were diagnosed with PGC. The pathological diagnosis of cancer was verified in all 23 patients.

Methods

Operative notes and pathology reports were examined to confirm free perforation of the stomach. Patients with GC penetrating the gastric wall but without peroration or peritoneal soiling or abscess formation were also excluded.The clinicopathological features of all patients were analyzed based on their medical records. The age, sex, preoperativeor intra-operative diagnosis,tumor location, histological classification, depth of gastric wall invasion, presence of lymph node metastasis, peritoneal dissemination, stage, initial surgical procedure,two stage gastrectomy, lymph node dissection, curability, postoperative complication, death in hospital, postoperative hospital stays, adjuvant chemotherapy, chemotherapy, radiation, cause of death, andsurvival durationfor patients with PGC were reviewed. In addition, we compared the findings of patients with GC perforation who underwent one- and two-stagegastrectomies.Finally, a survival analysis was performed. The parameters obtained from the medical records included the demographic data.

Evaluations

Clinical, surgical, and pathological findings were categorized according to the 15th Japanese Classification of Gastric Carcinoma (JCGC).The Union for International Cancer Control (UICC) R factor was applied for quantification: no residual cancer (R0), microscopically residual cancer (R1), and macroscopically residual cancer (R2), respectively.

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 the Mitoyo General Hospital (approval number, 22-CR01-258; approval date, March 17, 2023).

Statistical analyses

Statistical analyses were performed using the R software program, version 4.2.2, with the survivalpackage.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 the survival were determined using the log-rank test. All tests were 2-sided, and*p*values of <0.05 were considered statistically significant.

III. RESULTS

Clinical-pathologicalcharacteristics

All the patients were managed as a surgical emergency, and laparotomy was performed with a midline incision. The mean age of the 23 patients (18 male, 5female)was 68.6 (44-92)years old. In 14 patients (60.9%) of the 23 patients, the diagnosis of GC had been established preoperatively or intra-operatively. The tumor was in the upper third of the stomach in 3 (13.0%) patients, in the middle third of the stomach in 10 (43.5%) patients, and in the lower third of the stomach in 10 (43.5%) patients. The wall depth of tumor invasion was T3 (SS) in 2 (8.7%) patients, T4a (SE) in 19(82.6%) patients, and T4b (SI) in 2 (8.7%) patients. Lymph-node metastasis was N0 in2 (8.7%) patients, N1 in 7 (30.4%) patients, N2 in 6 (26.1%)patients, N3 in 3 (13.0%)patients, and Nx (unknown metastasis) in 5(21.7%) patients.The P-factor, an indicator of peritoneal dissemination, was P0 in 14 (60.9%) patients and P1 in 9(39.1%) patients. The stage was classified as follows: stage II (n= 2: 8.7%), stage III (n=8: 34.8%), and stage IV (n=13: 56.5%). The initial operations performed

were distal gastrectomy in 9 (39.1%) patients, total gastrectomy in 3 (13.0%) patients, and simple closure with an omental patch in 11 (47.8%) patients. The two-stage gastrectomies were distal gastrectomy in one patient and total gastrectomy in twopatients. Lymphadenectomy was classified as follows: D0 (n=8: 34.8%), D1 (n=6: 26.1%), and D2 (n=9: 39.1%). Curative resection R0 was performed in 10 (43.5%) patients, whereas non-curative R2 resection was performed in13 (56.5%) patients (Table 1).

Clinical outcome, treatment, and survival

The surgical and non-surgical complications were observed. Two (8.7%) patients had anastomotic dehiscence, 1 (4.3%) patient had respiratory failure, and 1 (4.3%) patient had sepsis.Two patients died in the hospital. One of the patients was in preoperative shock due to severe peritonitis and died of sepsis on the second day after surgery of simple closure with an omental patch. The other patient died of respiratory failure57 days after initial surgery of distal gastrectomy.The average postoperative hospital stay was 35 days.Adjuvant chemotherapy with S-1 was administered in two patients.Chemotherapy included S-1+Cisplatin(CDDP)was administeredin 11 patients, and radiation was performed in 2 patients with bone metastases.Cancer-related death was seen in 16 (69.6%) patients, and perforation-related death wasseen in 2 (8.7%) patients. The overall survival was 0-71(median:8)months(Table 2).

Characteristics of the two groups

There were no significant differences between the two groups in anycharacteristics(Table 3).

Factorsassociated with the survival and the prognosis

The cumulative 5-year survival rate was 62.1%. The survival rate ofthe 10 patients with curative R0 resectionsignificantly exceeded that of the 3 patients with non-curative R2 resection (p=0.0261)(Fig. 1).There was no significant differenceinthe survival rates between the 1- and the 2-stage gastrectomy groups(p=0.658) (Fig. 2).

IV. DISCUSSION

The management of PGC is still debated due to the lack of clinical guidelines supporting a specific algorithm in an emergency where surgery has a dual purpose: treating life-threatening peritonitis and curing GC. Even if GC can be diagnosed preoperatively or intra-operatively, the choice of treatment for PGC depends on several factors regarding emergency, oncologic, and patient variables, such as severity of peritonitis, hemodynamic instability, sepsis presence of comorbidity and presence of metastases on exploration (2).

In many emergent surgeries, a detailed examination, such as an intra-operative histological diagnosis using a frozen section or intra-operative endoscopy, could not be performed. Only 30.5% of patients were known to have GC before surgery (7). Ergulet al (8) reported that an older age and longer symptom duration, larger perforation size, and middle-upper third gastric perforations were likely to be associated with cancer etiology.

The preoperative or intra-operative diagnosis rate of PGC has been reported to be 29%-57% (7, 14),as inflammation can mimic cancer and lead to misinterpretation and overestimation of intra-operative findings. In the present study, we also were unable toperform any examinations, such as an intra-operative histological diagnosis using a frozen section or intra-operative endoscopy, due to the emergent nature of the surgery. However, we were able to perform a preoperative or intra-operative diagnosis of PGC in 14 (60.9%)of the 23 patients, which is better than the rates in previous reports.Previous studies found that 68%-72% of patients with PGC had stage III or IV disease (3, 15), and the overall mortality rate was 14.8%. In the present study, however, 21 (91.3%) patients had stage III or IV disease, and the overall mortality rate was 8.7%.

Due to the rarity of PGC, the risk of perforation cancer spreading remains unclear at present. Contrary to previous assumptions, it has recently been demonstrated that spillage of gastric juice containing viable cancer cells can occur and may cause peritoneal seeding (16). Historically, the presence of free GC cells in the peritoneum has been associated with a significant reduction in the survival after gastrectomy (17), and the long-term survival after gastrectomy for PGC was reported to be worse than in patients without perforation (6, 7). In the present study, peritoneal dissemination (P1) was observed in 9 (39.1%) patients during surgery, and peritoneal recurrence after surgery occurred in 3 patients.

Surgical treatment for PGC has two opposing purposes: to save the patient's life and control damage fromdiffuse peritonitis, and to remove malignant tissues without leaving any residual pieces behind. Several reports on PCG have shown a significantly better prognosis for patients who underwent curative resection thanin those who underwent non-curative resection (2, 10, 12, 18, 19). In the preset study, we performed curative R0 gastrectomy in 8 (66.7%) of 12 patients who underwent1-stage gastrectomy and in 2 (66.7%) of 3 patients who underwent 2-stage gastrectomy. We feel that we should endeavor to increase the rate of curative R0 resection in

one- and two-stage gastrectomies and improve the survival of the patients with PGC in the future.

The survival rate in the present study was significantly better for patients who underwent curative R0 resection than for those who underwent non-curative R2 resection, regardless of whether the surgical approach was one-or two-stage gastrectomy. Furthermore,curative R0 resection was an important prognostic factor. Although curative R0 resection by one-stage gastrectomy is necessary for achieving the dual purpose of treating peritonitis caused by gastric perforation and resecting gastric malignancy, there are many patients who did not undergo curative R0 resection at the initial surgery due to severe peritonitis or an insufficient examination (6).For such cases, two-stage gastrectomy can improve the possibility of achieving curative R0 resection in the future after recovering from the severe peritonitis or undergoing a detailed sufficient examination.

Lehnert et al (11) defined the criteria for one-stage gastrectomy as follows: (1) when GC has been diagnosed; (2) when a patient's general condition is good and there is no risk of surgical complications; and (3) when peritonitis is not severe. In the present study, eight patients underwent simple closure with an omental patch at the initial surgery, with noneshowingleakage from the site of closure. In addition, three patients who underwent two-stage gastrectomy showed no postoperative complicationsor hospital death.

As a general recommendation, we can conclude that the best results in terms of the surgical outcome and overall survival are obtained when the treatment strategy is tailored to the general condition of patients, especially regarding the extent of peritonitis; a balance between oncologic and emergency criteria should be the guiding light for the treatment choice, which should be made on a case-by case bias. One- or two-stage gastrectomy with curative R0 resection intent should always be selected if technically feasible when GC is suspected, even when a definitive pathology is not provided. However, simple closure with an omental patch can be considered instead of gastrectomy when life-threatening conditions are present.

For PGC, a laparoscopic approach for the initial surgery can be useful, as it facilitates observing the whole abdominal cavity, which might be difficult in cases of open laparotomy. Laparoscopic management in PGC provides beneficial gains in surgical performance. With the oncological advantage of two-stage gastrectomy, the laparoscopic approach might be considered as an alternative treatment for PGC (20). Most emergency surgeries for PGC are not performed by GC specialists. Therefore, it is very difficult to perform primary gastrectomy with curative intent as an emergency surgery. Laparoscopic primary gastrectomy is thus only recommended as an emergent surgical method when it can be performed by an expert (18).

Several limitations associated with the present studywarrant mention. First, the study was a relatively long-term retrospective study due to the low incidence of PGC and a small number of patients. Second, the number of cases was insufficient for a statistical analysis.

V. CONCLUSIONS

Regardless of whether patients underwent one- or two-stage gastrectomy, curative R0 resection improved the survival in patients with PGC. The best surgical approach for PGC is one that can increase the probability of safely achieving curative R0 resection to the greatest extent, and the surgeon's decision on whether to perform one-or two-stage gastrectomy should be made based ontheir perspective.

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

Authors' 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.

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All data generated or analyzed during this study are included in this published article.
Ethics approval and consent to participate
None
Consent for publication
Consent to publish was obtained from the patient.

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Figure Legends
Fig. 1. The survival rate ofthe 10 patients with curative R0 resectionsignificantly exceeded that of the 3 patients with non-curative R2 resection (p=0.0261).
Fig. 2. There was no significant difference in the survival rates between the 1- and 2-stage gastrectomy groups(p=0.658).

Table 1. Clinicopathological characteristicsand surgical outcomes
Table2. Clinical outcomes, treatment, and the survival
Table 3. Clinicopathological characteristics and surgical outcomes of perforated gastric cancer (one- or two-stage gastrectomy)

Table 1

Variable	Number of patients (n=23) (%)
Ages	
Range (years)/mean	44-92 (68.6)
Gender	
Male	18 (78.3)
Female	5 (21.7)
Preoperative or inraoperateve diagnosis	
Perforation	9 (39.1)
Cancer	14 (60.9)
Tumor location	
U	3 (13.0)
M	10 (43.5)
L	10 (43.5)
Histological classification	
Differentiated type	6 (26.1)
Undifferentiated type	17 (73.9)
T factor	
T3	2 (8.7)
T4a	19 (82.6)
T4b	2 (8.7)
N factor	
N0	2 (8.7)
N1	7 (30.4)
N2	6 (26.1)
N3	3 (13.0)
Nx	5 (21.7)
P factor	
P0	14 (60.9)
P1	9 (39.1)
Stage	
II	2 (8.7)
III	8 (34.8)
IV	13 (56.5)
Initial surgical procedure	
Distal gastrectomy	9 (39.1)
Total gastrectomy	3 (13.0)
Simple closure with an omental patch	11 (47.8)
Two-stage gastrectomy	3 (13.0)

Distal gastrectomy	1 (4.3)
Total gastrectomy	2 (8.7)
Lymph node dissection	
D0	8 (34.8)
D1	6 (26.1)
D2	9 (39.1)
Curability	
Curative (R0)	10 (43.5)
Non- curative (R2)	13 (56.5)

Differentiated type: papillary adenocarcinoma, tubular adenocarcinoma
Undifferentiated type: poorly differentiated adenocarcinoma, signet-ring cell adenocarcinoma, mucinous adenocarcinoma

Table 2

Variable	Number of patients (n=23) (%)
Postoperative complication	
Anastomotic dehiscence	2 (8.7)
Respiratory failure	1 (4.3)
Sepsis	1 (4.3)
Death in hospital	2 (8.7)
Postoperative hospital stay	
Range (days) /mean	2-57 (31.2)
Adjuvant chemotherapy	2 (8.7)
Chemotherapy	11 (47.8)
Radiation for bones	2 (8.7)
Cause of death	
Cancer-related	16 (69.6)
Perforation-related	2 (8.7)
Survival duration	
Range (months) / median	0-71 (8)

Table 3

Characteristics	One-stage gastrectomy (n=12) (%)	Two-stage gastrectomy (n=3) (%)	*p* value
Mean age (years)	71.4	67.7	0.648
Gender			0.661
Male	8 (66.7)	3 (100)	
Female	4 (33.3)	0	
Tumor location			0.897
M	5 (41.7)	2 (66.7)	
L	7 (58.3)	1 (33.3)	
Histological classification			0.661
Differentiated type	3 (25)	1 (33.3)	
Undifferentiated type	9 (75)	1 (33.3)	
T factor			0.849
T3	1 (8.3)	1 (33.3)	
T4	11 (91.7)	1 (33.3)	
N factor			0.696
N0	2 (16.7)	0	
N1	6 (50)	1 (33.3)	
N2	1 (8.3)	1 (33.3)	
N3	3 (25)	1 (33.3)	
P factor			0.494
P0	8 (66.7)	2 (66.7)	
P1	4 (33.3)	1 (33.3)	
Stage			0.684
II	2 (16.7)	0	
III	6 (50)	2 (66.7)	
IV	4 (33.3)	1 (33.3)	
Postoperative complications			0.812
None	9 (75)	3 (100)	
Anastmotic failure	2 (16.7)	0	
Respiratory insufficiency	1 (8.3)	0	

Fig. 1

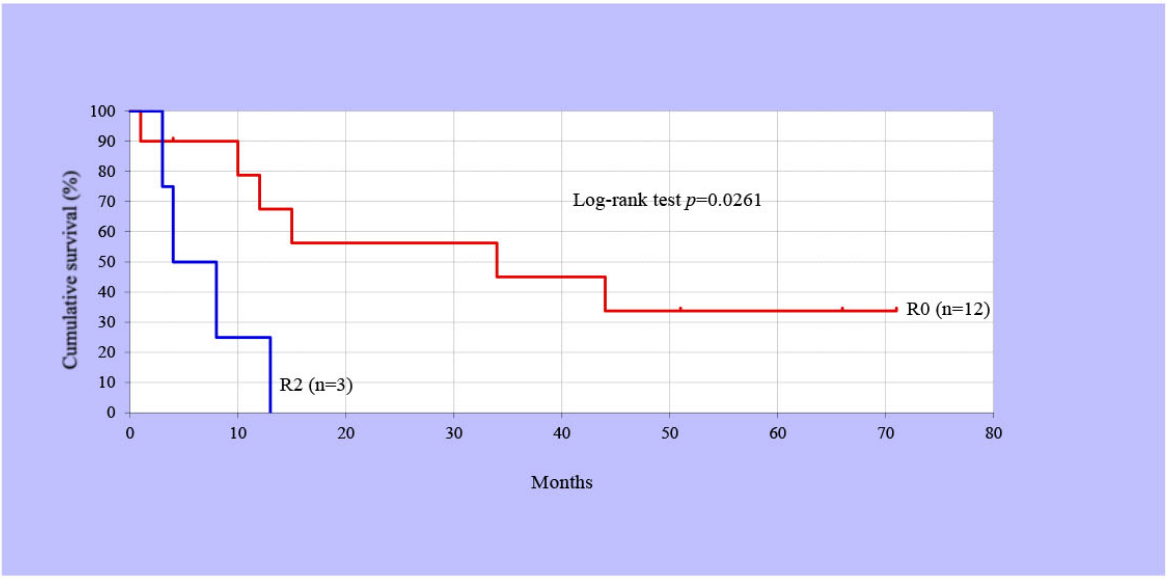
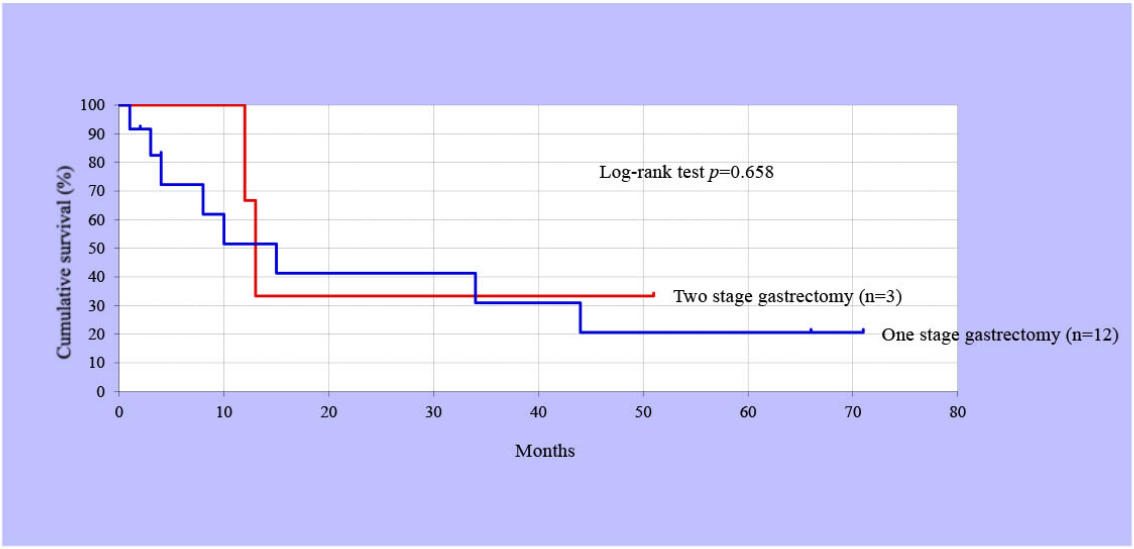

Cumulative survival (%)
100
90
80
70
60
50
40
30
20
10
0
0
10
20
30
40
50
60
70
80
Months
Log-rank test p=0.0261
R0 (n=12)
R2 (n=3)

Fig. 2


Cumulative survival (%)
100
90
80
70
60
50
40
30
20
10
0
0
10
20
30
40
50
60
70
80
Months
Log-rank test p=0.658
Two stage gastrectomy (n=3)
One stage gastrectomy (n=12)