

Feasibility of a “Stomach-preserving Strategy” for Perforated Gastric Cancer in Patients With Distant Metastasis

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Abstract

Background/Aim: Gastrectomy is often performed for perforated gastric cancer in patients receiving treatment with curative intent. However, gastrectomy is not a curative procedure, precludes oral intake, and may hinder palliative chemotherapy in patients with metastatic disease. The present study assessed the feasibility of a “stomach-preserving strategy” comprising peritoneal lavage and repair surgery for the management of gastric cancer perforation in patients with distant metastasis.

Patients and Methods: We retrospectively reviewed the medical records of patients with gastric cancer who underwent surgical treatment at our hospital from 2013 to 2021. The clinical courses of patients who had undergone peritoneal lavage and repair surgery for perforated gastric cancer with distant metastasis were reviewed to evaluate postoperative outcomes.

Results: During the study period, 3,862 patients underwent radical gastrectomy. Additionally, nine patients with stage IV gastric cancer with distant metastasis prior to treatment underwent emergency surgery due to gastric perforation. Of the nine patients that underwent emergency surgery, seven patients underwent peritoneal lavage and repair surgery and two underwent peritoneal lavage only. No cases of secondary leakage were observed. Seven patients (78%) had a good postoperative course including the resumption of meals and continuation of chemotherapy. The remaining two died of sepsis. The median overall survival time was five months from surgery and 12 months from the initiation of palliative chemotherapy.

Conclusion: A “stomach-preserving strategy” for the management of perforated gastric cancer is safe in patients with stage IV gastric cancer with distant metastasis and allows continuation of oral intake and palliative chemotherapy.

Keywords: Gastric cancer, distant metastasis, perforation, stomach-preserving.



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Introduction

Gastric perforation is primarily caused by spontaneous perforation of a peptic ulcer precipitated by the use of nonsteroidal anti-inflammatory drugs or *Helicobacter pylori* infection (1, 2). While the incidence of gastric perforation has dramatically declined following the advent of acid-suppressing agents, such as proton pump inhibitors (PPIs), and the development of *H. pylori* eradication strategies, cases of gastric perforation requiring surgical treatment still occur.

In benign cases of gastric perforation caused by peptic ulcer disease, nonoperative management is possible in patients with a stable clinical condition; however, a proportion of cases require surgical intervention for perioperative resuscitation and management of sepsis (3, 4). In contrast, malignant gastric perforation is a typical manifestation of advanced gastric cancer with serosal invasion or distant metastasis (5). In addition, ramucirumab (RAM), a VEGFR2 antagonist that binds to VEGFR2 and inhibits VEGF-mediated tumor angiogenesis, increases the risk of gastric perforation (6). Unlike in cases of benign gastric perforation, conservative management with PPIs is not appropriate in cases of malignant gastric perforation. Accordingly, peritoneal lavage for peritonitis or gastrectomy should be considered in cases of perforated gastric cancer (7).

Perforation of the stomach due to gastric cancer typically occurs in patients with large and advanced tumors, which may be accompanied by distant metastasis. The mainstay of treatment is systemic chemotherapy for gastric cancer with distant metastasis. The Japanese treatment guidelines recommend several palliative chemotherapy regimens based on the results from randomized controlled trials (8). The survival benefits of palliative gastrectomy remains controversial in patients with unresectable advanced gastric cancer (9, 10). Moreover, postoperative complications and functional impairment following gastrectomy decrease compliance with chemotherapy and lower quality of life (QOL) (11, 12). Additionally, a recent study showed that the presence of distant metastasis increased the rates of overall

complications (13). Accordingly, there is a need for the development of novel strategies that do not involve gastrectomy for the management of gastric perforation in patients with distant metastasis. Palliative gastrectomy can be avoided if peritonitis is managed by repair surgery, such as simple closure and omental patching with peritoneal lavage. This “stomach-preserving strategy” may be particularly beneficial for patients with perforated gastric cancer having distant metastasis as it avoids unnecessary invasive procedures, facilitates palliative chemotherapy, and improves QOL.

The purpose of the present study was to assess the feasibility of a “stomach-preserving strategy” for the management of perforated gastric cancer in patients with distant metastasis.

Patients and Methods

We retrospectively reviewed the medical records of patients with gastric cancer who underwent surgical treatment at Cancer Institute Hospital of Japanese Foundation for Cancer Research from April 2013 to December 2022. Patients who had undergone surgical treatment for perforated stage IV gastric cancer with distant metastasis were included in the study analysis. The analysis included clinicopathological features, such as age, sex, tumor location, depth of gastric wall invasion, lymph node metastasis, distant metastasis, administration of palliative chemotherapy, palliative chemotherapy regime, and type of surgery. Surgical and postoperative outcomes were also evaluated. Tumor-node-metastasis staging was applied according to the 14th edition of the Japanese Classification of Gastric Carcinoma (3rd English edition) (14). Emergency surgery was conducted in patients able to tolerate general anesthesia. The policy at our hospital during the study period was the use of peritoneal lavage and repair surgery, such as simple closure and omental patch repair, rather than gastrectomy where possible.

Ethics. This study was approved by the Institutional Review Board of the Cancer Institute Hospital (2023-GB-

Table I. Clinicopathological backgrounds of the patients with perforated cStage IV gastric cancer with distant metastasis.

Case	Sex	Age	Main tumor location	Tumor size (mm)	T category	M factor	Chemotherapy before the perforation	Duration between the initiation of the chemotherapy to the perforation (months)
1	M	55	M	150	T4a	Peritoneum	LV+5-FU	4
2	F	66	M	100	T4a	Peritoneum	None	—
3	M	75	M	60	T4b	Peritoneum	SOX	2
4	F	70	L	80	T4a	Distant lymph node	SOX	<1 (3 days)
5	M	84	L	120	T4a	Peritoneum	S-1/SOX/RAM+nab-PTX	8
6	F	57	L	60	T4a	Peritoneum	SP+ip PTX/RAM+nab-PTX	7
7	M	54	M	70	T4a	Peritoneum	SOX/PTX	2
8	M	71	M	120	T4b	Peritoneum	SOX/RAM+nab-PTX	7
9	F	70	M	100	T4a	Peritoneum	SP	<1 (15 days)
10	F	65	M	80	T4a	Peritoneum	SOX+Nivolumab	<1 (14 days)

LV: Leucovorin; 5-FU: 5-fluorouracil; SOX: S-1+Oxaliplatin; RAM: ramucirumab; PTX: paclitaxel; ip: intraperitoneal; SP: S-1+cisplatin.

091). All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent or an equivalent was obtained from all patients.

Statistical analysis. The Kaplan-Meier method was used to generate survival curves. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

Results

During the study period, 3,862 patients underwent gastrectomy with curative intent. In addition, ten patients with stage IV gastric cancer with distant metastasis underwent emergency surgery due to gastric perforation. The clinicopathological features of the ten patients that underwent emergency surgery are presented in Table I. Five patients that underwent emergency surgery were male and the remaining five were female, with an overall median age of 68 years. Seven (70%) perforations occurred in the middle third of the stomach. The median

tumor size was 90 mm. All patients were preoperatively diagnosed with stage IV gastric cancer with distant metastasis due to peritoneal metastasis (n=9) or distant lymph node metastasis (n=1). Eight patients (80%) had already initiated chemotherapy when gastric perforation occurred. Three cases (cases 5, 6, and 8) had received RAM. The median period from the initiation of chemotherapy to gastric perforation was two months.

Table II summarizes the surgical outcomes in patients that underwent emergency surgery. Five patients (50%) underwent laparoscopy, and five patients underwent laparotomy. Eight patients underwent repair surgery with peritoneal lavage and two patients (cases 1 and 7) underwent peritoneal lavage only as the omentum was already adhered to and covering the perforation defect. Four patients (cases 2, 3, 4, and 9) underwent simultaneous enterostomy. The median operation duration was 175 min, and the median estimated blood loss was 5 ml. Two patients (cases 1 and 5; 20%) did not recover from sepsis.

Postoperative outcomes are shown in Table II. Eight patients (cases 2, 3, 4, 6, 7, 8, 9, 10; 80%) had good postoperative courses, recovering sufficiently to resume meals and continue chemotherapy. Four out of eight patients who underwent enterostomy (cases 2, 3, 4, and

Table II. Surgical data and postoperative outcomes of cStage IV perforated gastric cancer with distant metastasis.

Patient No.	Approach	Operation	Enterostomy	Operation time (min)	Blood loss (ml)	Postoperative complications	Time to initial oral intake (days)	Hospitalization (days)	Postoperative chemotherapy	Survival* (months)
1	Laparoscopic	PL	No	69	2	Died of sepsis	—	19**	No	4
2	Open	PL+RS	Yes	144	15	None	11	22	Yes	4
3	Open	PL+RS	Yes	235	70	None	12	36	Yes	16
4	Laparoscopic	PL+RS	Yes	206	0	None	10	17	Yes	5***
5	Open	PL+RS	No	211	0	Died of sepsis	—	65**	No	12
6	Laparoscopic	PL+RS	No	237	10	None	14	33	Yes	15
7	Laparoscopic	PL	No	94	0	None	9	50	Yes	4
8	Open	PL+RS	No	112	10	None	14	31	Yes	12
9	Open	PL+RS	Yes	224	2	None	14	23	Yes	7***
10	Laparoscopic	PL+RS	No	144	20	None	12	52	Yes	7

PL: Peritoneal lavage; RS: repair surgery. *From initiation of chemotherapy to death; **in-hospital death; ***dropped out of follow-up.

9; 50%) were able to resume enteral feeding from the first postoperative day. The median period from surgery to the resumption of meals was 12 days. The length of hospital stays for patients with enterotomy tended to be shorter than that for those without (22.5 vs. 41.5 days, $p=0.179$). The median overall survival was six months from surgery and 12 months from the initiation of chemotherapy (Figure 1).

Discussion

Perforated gastric cancer is a rare occurrence. However, patients with advanced gastric cancer are at increased risk of gastric perforation due to malignant invasion and the use of RAM, as in cases 5, 6, and 8. Accordingly, there is a need for the establishment of strategies for the management of perforated gastric cancer given the ongoing debate regarding optimal strategies and the lack of clinical guidelines. The management of perforated gastric cancer is particularly challenging in patients with stage IV gastric cancer with distant metastasis as the need for gastrectomy is uncertain. However, few studies have evaluated strategies for the management of perforated gastric cancer in patients with distant metastasis (15, 16). As a result, the utility and benefits of alternative approaches to palliative gastrectomy, such as peritoneal lavage and repair surgery, remain uncertain. In the present study, we reviewed the clinical outcomes of nine patients with stage IV gastric cancer with distant metastasis that received treatment for gastric perforation according to a “stomach-preserving strategy”.

Secondary leakage is a major complication of repair surgery for perforated gastric cancer (17). Inflamed and tumor-infiltrated tissues are particularly vulnerable to postoperative complications (18). Previous studies have reported high procedure-related mortality in patients undergoing repair surgery for perforated gastric cancer, due to the secondary leakage (19). In contrast, no case of secondary leakage was observed in our series. This finding may be attributable to the use of early postoperative feeding by enterostomy. When repair surgery was performed, the resumption of oral feeding was delayed

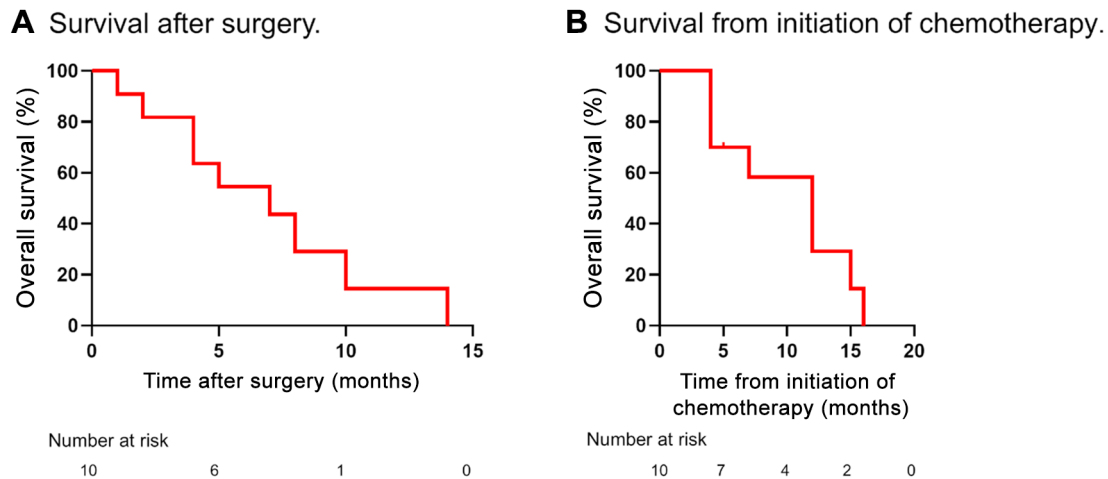


Figure 1. Kaplan-Meier estimates of overall survival (A) after surgery and (B) from initiation of chemotherapy.

compared to gastrectomy (median, 12 days), even in patients with a good postoperative course. In the present study, four out of the eight patients (50%) who were successfully discharged underwent simultaneous enterostomy. Additionally, the patients who underwent simultaneous enterostomy had shorter hospital stays than those who did not undergo enterostomy. As delayed resumption of feeding and malnutrition are risk factors for postoperative complications (20), the nutritional support provided to the four patients who underwent enterostomy may have decreased the risk of secondary leakage and allowed their quick recovery. Although some cases in the present study did not undergo enterostomy due to the surgeon's decision, simultaneous enterostomy should be considered in cases of perforated gastric cancer.

The results of the present study demonstrate that perforated gastric cancer can be managed with peritoneal lavage and repair surgery, thereby avoiding gastrectomy, in patients with stage IV gastric cancer with distant metastasis. Several previous studies have reported superior results for radical gastrectomy compared to repair surgery; however, most patients who underwent repair surgery in these studies had poor general condition, thereby inevitably introducing selection bias (21, 22). In the present study, approximately 80% of patients that underwent surgery had

no postoperative complications and sufficiently recovered to allow the resumption of meals and chemotherapy. In addition, the median overall survival from the initiation of chemotherapy was approximately 12 months, comparable to the reported survival in patients with gastric cancer treated with palliative chemotherapy (23). These results indicate that a "stomach-preserving strategy" may be beneficial for the treatment of perforated gastric cancer in patients with distant metastasis.

Two patients who underwent emergency surgery in the present study (20%) had unfavorable outcomes. Both cases 1 and 5 in the present study underwent peritoneal lavage but died of disseminated intravascular coagulation due to extensive peritonitis. The peritonitis of patients with stage IV gastric cancer easily deteriorates because most of them are receiving chemotherapy, in which general clinical condition and disease progression rather than surgical strategy are often the key determinants of postoperative mortality. At our institution, we selected a "stomach-preserving strategy" to all stage IV gastric cancer cases; therefore, we could not compare our results with those undergoing palliative gastrectomy or those treated with conservative treatment. However, several previous studies reported the high risk of gastrectomy for perforated gastric cancer;

including a postoperative complication rate of 35%-46% and 30-day mortality of 25%-46% (12, 18, 24-27). Thus, we speculated palliative gastrectomy might have poor outcomes considering its invasiveness and high risk of morbidity and mortality.

Study limitations. First, this was a retrospective study conducted at a single institution. Accordingly, selection bias could not be eliminated when deciding on operative indications and treatment options. Second, the surgical procedures used may have varied as different surgeons operated on different cases, and this difference may have affected postoperative outcomes. Finally, data were collected over a long period of time. Accordingly, chemotherapy regimens may have changed over this period, thereby affecting survival. However, unlike preoperative chemotherapy of curable cancers, the choice of chemotherapy for stage IV gastric cancer with distant metastasis is complex and depends on individual patient factors. Although the present study had these inevitable limitations, our findings may be beneficial as there is little evidence regarding the use of a “stomach-preserving strategy” for the management of perforated gastric cancer in patients with distant metastasis.

Conclusion

In patients with stage IV gastric cancer with distant metastasis, the use of a “stomach-preserving strategy” for the management of perforated gastric cancer may allow the continuation of oral intake and palliative chemotherapy while avoiding unnecessary gastrectomy.

Funding

None.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

Conception & design; MT, KK, and SN, acquisition of data; MT, analysis and interpretation of data; MT, KK, and SN, drafting article; MT, KK, and SN, revising it critically; All Authors, final approval of the version; All Authors.

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