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Perforated Gastrıc Cancer: A Difficult Challenge For The Surgeon

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ABSTRACT

Perforated gastric cancer (PGC) is a rare complication of gastric cancer that is associated with high in-hospital mortality. Most patients with PGC undergo emergency surgery with a prediagnosis of acute abdomen. The challenges faced in the preoperative diagnosis persist during surgery due to lack of an optimum surgical approach, meaning that the surgical treatment of patients with PGC is often based on the experience and prejudices of the surgeon. The aim in the present study is to evaluate the clinicopathological characteristics of patients with PGC and to discuss the currently available surgical treatment options.

The present study investigated retrospectively the demographic characteristics of 30 patients who underwent surgery for pgc in our clinic, and in whom a pathological examination revealed adenocarcinoma. The study further evaluated the relationship between the employed treatment methods and survival.

The study included 30 patients, 23 of which were male and seven who were female. The mean age was 62.4±10.5 years. In terms of disease progression, 23 patients had stage IV, six had stage III and one had stage II. Of the total, 19 patients underwent a gastrectomy and 11 underwent local repair. In-hospital mortality occurred in 10 patients (four of which underwent a gastrectomy and six who underwent a local repair). The difference between the gastrectomy and local repair groups was significant in terms of mortality ($p<0.017$). Overall survival was 286±516.7 days across the entire study group, 421.2±614.8 days in the gastrectomy group and 68±105.7 days in the local repair group. There was a significant difference between the two groups in terms of mean survival ($p<0.13$). A positive correlation was identified between perioperative sepsis parameters and in-hospital mortality. The mean survival time was significantly higher in the non-septic group (886±729.5 days) than in the septic group (67.8±65.5 days) ($p<0.01$).

Patients with PGC represent a challenge for surgeons due to difficulties in treatment and the poor prognosis of the patients. Although PGC occurs in only very rare occasions, it must be kept in mind that the selection of an appropriate surgical therapy and the successful treatment of sepsis are of vital importance.

Key Words: Perforated gastric cancer, gastrectomy

Introduction

Oncological emergencies occurring in patients with gastric cancer include major hemorrhage and tumor perforation. Incidences of perforation in patients with gastric cancer range between 0.3% and 3.9%, and they are associated with high mortality. In literature, the most common cause of gastric perforations is benign gastric ulcers. Gastric cancers are the cause of gastric perforations in approximately 10–16% of patients (1,2). Perforated gastric cancers (PGCs) can be challenging in preoperative diagnosis, as the symptoms of PGCs resemble those of a perforated gastric ulcer (1). Thus, only one third of patients with PGC can be diagnosed preoperatively. Benign causes cannot be differentiated from malignancies in most cases during surgery, and a diagnosis of malignancy can only be established through a postoperative pathological examination of the specimen (3).

A surgeon encountering a patient with a PGC faces a challenge in deciding which surgical strategy to follow. Unfortunately, there is no widely accepted standardized treatment method and there is a continuing debate in this respect. The selected treatment method should resolve peritonitis, which is responsible for emergency presentation, and any gastrectomy should comply with the oncologic technical aspects of surgery. For this purpose, surgery can be performed in a single- or two-stage approach (4).

In a single-stage approach, the cleansing of the peritoneum and a gastrectomy and lymphadenoectomy of the malignant tumor are performed in the same session. This two-stage approach aims to manage the life-threatening peritonitis in the first session, while the gastrectomy and lymph node dissection are

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performed in accordance with oncological principles in the second stage (1,3). The prognosis of PGC is poor, regardless of the surgical technique employed. The leading cause of a poor outcome is often the presence of an advanced-stage tumor resulting in a perforation, and the presence of generalized peritonitis caused by perforation (5).

Material and Methods

The present study investigated retrospectively the demographic characteristics of the patients, as well as the methods employed for their treatment, who underwent surgery in our clinic for gastric cancer. The study included patients with a pathological diagnosis of adenocarcinoma. Those with perforations secondary to malignancies other than adenocarcinomas were excluded from the study. The study included 17 new patients who were treated in our clinic, in addition to 13 patients who were evaluated previously by Kotan et al. (5) at the same clinic. Age, gender, perioperative diagnoses (perforation/cancer), localization of perforation, lymph nodes and presence of distant metastasis, surgical technique employed, degree of lymph node dissection, resection margin (R0, R1, R2) according to the FNCLCC system and length of hospital stay were all evaluated. The effect of the presence of systemic inflammatory response syndrome (SIRS) and sepsis on in-hospital mortality was also evaluated.

Statistical Analysis: Descriptive statistics of the continuous variables obtained from the study groups included median, mean, standard deviation, and minimum and maximum values. A Shapiro-Wilk test ($n<50$) was used to test the normality of distribution of the primary variable, and nonparametric tests were used, as the variables were not normally distributed (Table 1). Mann Whitney U test was used to compare the groups in pairs and to evaluate the differences between the groups. The level of statistical significance in the calculations was set at an alpha of 5% (α) and the SPSS (IBM SPSS for Windows, ver. 24) statistical software package was used for the calculations. (Table 1)

Results

A total of 30 patients with a PGC who were treated between 2000 and 2018 were included in the study. Clinicopathological data of the study group, which was composed of 23 males and seven females with a mean age of 62.4±10.5 years, was obtained (Table 2). PGC constituted 4.8% of all gastric cancers and 6% of all gastric perforations; seven patients were diagnosed with gastric cancer before surgery, two of which were considered inoperable, and three sustained a perforation of the gastric tumor while receiving neoadjuvant chemotherapy. Apart from these patients, six patients who underwent a preoperative computed tomography were found to be suspicious for malignancy. Preoperative diagnoses were only gastrointestinal perforation in 17 patients; 23 patients had stage 4, six had stage 3 and one had stage 2 of the disease. The localization of the perforation was cardia in nine patients, corpus in 11 patients and antrum in 10 patients. (Table 2)

Patients who were found to have a resectable disease underwent a total/subtotal gastrectomy in the same session. Patients with a poor general condition, an extensive tumor and severe peritonitis, and those in whom technical difficulties were encountered during resection underwent local repair+omental patch. No radical lymph node dissection together with a curative resection could be performed in any of the patients.

Of the total, 27 patients underwent single-stage surgery and three patients underwent two-stage surgery; 19 patients (63%) underwent a gastrectomy and 11 patients (37%) with a poor general medical condition and with a local invasion interfering with a resection underwent palliative surgery. Palliative surgery involved primary repair with the omental patch technique, and one patient in the local repair group was treated with a tube gastrostomy. Of the patients undergoing primary repair, three experienced cardiac arrest during the induction of anesthesia prior to surgery, and no local repair could be made in these patients after cardiopulmonary resuscitation. All three patients died postoperatively in the intensive care unit.

Of the 19 patients who underwent a total gastrectomy, 13 (43%) underwent emergency total gastrectomy and six (20%) underwent a distal subtotal gastrectomy (DSG). A limited lymph node dissection including perigastric lymph nodes could be performed in only three patients in the total gastrectomy group. A 3-cm mass was detected in the head of the pancreas of one patient. As the general condition of this patient deemed them unable to tolerate extensive surgery, choledochotomy and hepaticojejunostomy were added to gastrectomy. Of the patients who underwent TG, three had hepatic metastasis, one

Table 1. Tests of Normality

	Kolmogorov-Smirnov			Shapiro-Wilk		
	Statistics	df	Sig.	Statistics	df	Sig.
Age	.129	30	.200*	.945	30	.124
Survival	.358	30	.000	.572	30	.000
Length of Hospital Stay	.264	30	.000	.813	30	.000

had positive proximal surgical margins and all patients had a residual disease at a microscopic or macroscopic level (R1 or R2).

In the DSG group, five patients had macroscopic residual disease (R2) due to extensive tumor invasion. Although one patient had no macroscopic residual tumor tissue, a limited lymphadenectomy was performed in this patient due to severe peritoneal inflammation. This patient was then advised to undergo a second surgery for a complementary lymphadenectomy; however, the patient declined revision surgery. One patient underwent an R0 resection.

Furthermore, three patients underwent a two-stage treatment. The first and second surgeries of two patients were performed at our clinic and a DSG was performed after the primary repair. The first and second surgeries of the other patient had been performed at another center, and this patient was referred to our clinic due to anastomotic leakage, and underwent a total gastrectomy.

Anastomotic leakage was detected in three patients, of which two died in the hospital at days 22 and 32 after surgery, and the third died on day 85 after discharge. One patient who developed a pleural effusion underwent a tube thoracostomy, and this patient was discharged on postoperative day nine without further problems.

In-hospital mortality was observed in 10 patients (33%), and of these patients, four underwent a gastrectomy and six underwent local treatments. The mortality rate was significantly different between the gastrectomy and local repair groups ($p<0.017$).

The mean survival time was 421.2±614.8 days in the gastrectomy group and 68±105.7 days in the local repair group. There was a statistically significant difference between the two groups in terms of survival ($P<0.13$). No statistically significant difference was identified between the two groups in terms of the length of hospital stay (Table 3).

When the patients were divided into two groups according to their perioperative septic findings as septic patients and non-septic patients, a positive correlation was observed between the parameters of sepsis and in-hospital mortality. Mean survival was significantly higher in the non-septic group than in the septic group ($p<0.01$), being 886±729.5 days in the non-septic group and 67.8±65.5 days in the septic group. There was no statistically significant difference between the two groups in terms of the length of hospital stay (Table 4).

Discussion

Gastric perforation is a rare complication of gastric cancers, with a prevalence rate of less than 5% (6). It is not easy to differentiate between malignant tumor perforations and benign gastroduodenal or other hollow organ perforations due to the similar clinical presentation and symptoms. A preoperative diagnosis can be established in only one-third of patients as a result of these similarities. Furthermore, the only criterion that can be useful in a differential diagnosis is the patient's age (6). In particular, patients aged 60 years and older should be regarded as a high risk group for malignancy, and a high index of suspicion for malignancy must be maintained (7). The age range in our patient group was 39-77 years with a mean age of 62.4±10.5 years. It must be kept in mind, however, that perforated gastric cancer can be found also in young patients

The main goal in surgical treatment of PGC is to achieve a curative R0 resection, as is the case in the classic treatment of gastric cancer. As might be expected, patients undergoing R0 resection have a longer life expectancy. Mahar et al. reported a median survival of 75 months and a 5-year survival rate of 50% in a study of patients with PGC undergoing a curative resection (8). Furthermore, their study found better recovery in patients undergoing an R0 resection than in patients undergoing an R1 and R2 resection independent of a single-stage or two-stage gastrectomy.

Perforated gastric cancers pose preoperative, postoperative and intraoperative challenges to the

Table 2. Clinicopathological features of patients with perforated gastric cancer

Parameter	patients
Age	
Range (yr)/Mean	62.4 ± 10.5
Sex	
Female	7 Patients
Male	23 Patients
Mean LOS	16.3 Days
Gastrectomy	19.1±15.3
Primary repair	11.7±8.3
Preoperative diagnosis	
Perforation	23
Cancer	7
Location-Perforation site	
Lower third	10
Middle third	11
Upper third	9
Serosal invasion	
Absent	7
Present	23
Lymph node metastasis	
Absent	3
Present	27
Stage of disease	
I	None
II	1
III	6
IV	23
Surgery	
Gastrectomy	19
Total	13
Subtotal	6
Local repair	11
Lymph node dissection	
Extended (D2, D3)	0
Limited (D0, D1)	3
In-hospital mortality	10
Mean survival	286 ± 516.7
Gastrectomy	421.2±614.8
Local repair	68±105.7

surgeon. The main basis of these challenges is the inability to differentiate between perforations of benign causes from those of malignant causes, and therefore the complexity in the treatment processes. Although malignancy has been diagnosed preoperatively in such patients, evaluating the real size of the tumor and local resectability is not straightforward. Inflammatory changes secondary to diffuse peritonitis that often occurring in these patients interfere with the accurate intraoperative evaluation of local tumor infiltration and the sizes of lymph node metastases, and can even result in an overestimation of the actual situation in most

Table 3. According to the surgical method employed

		Median	Mean	Standard Deviation	Minimum	Maximum	*p.
Survival	Gastrectomy	180.00	412.21	614.89	1.00	1978.00	.013
	Local repair	19.00	68.00	105.74	3.00	360.00	
LOS	Gastrectomy	13.00	19.16	15.33	1.00	60.00	.081
	Local repair	9.00	10.73	8.53	3.00	31.00	

*Mann-Whitney U Test

Table 4. Effect of sepsis on length of survival and hospital stay

		Mean	Median	Standard Deviation	Minimum	Maximum	*p.
Survival	SEPSIS 0	886.00	646.50	729.51	190.00	1978.00	<.001
	1	67.82	45.00	65.56	1.00	205.00	
Length of Hospital Stay	SEPSIS 0	14.25	12.50	6.78	9.00	30.00	.605
	1	16.73	11.50	15.58	1.00	60.00	

*Mann-Whitney U-Test

cases (9). Some authors have suggested adopting a two-stage surgical procedure for PGC in order to resolve the conflicts and standardize the treatment. The first stage should target the surgical repair of the perforation and the prevention of peritonitis; while the second stage of surgery must be performed after the resolution of peritonitis and sepsis. The surgeon must proceed to the second stage only if a diagnosis of malignancy has been confirmed histopathologically and the patient is eligible for radical oncologic surgery (9).

There are also authors advocating the use of single-stage surgery over two-stage surgery in achieving palliation (10-12), suggesting that leakage can occur from the perforation site that is closed with local repair due to tissues being fragile and the poor wound healing caused by the tumor (2). These authors also state that dense adhesions secondary to previous peritonitis and initial surgery will complicate second surgery (11). For all of these reasons, they suggest that a gastrectomy with an extensive lymphadenectomy can achieve palliation if the general condition of the patient is suitable for such surgery. Despite this notion, a single-stage gastrectomy was reported to be associated with a high mortality rate (11.4%) and a low curative resection rate (50%) in a series of Japanese patients with PGC (3).

Whether caused by a malignant or benign process, Roviello et al. recommend a palliative or curative gastrectomy if the patient's general condition is good, that is to say, showing no signs of shock or localized peritonitis, and the absence of comorbidities. They suggested performing a primary closure in the first stage in patients with a poor general condition but with a curable disease, and postponing definitive surgery to the second session. Xiong et al. recommend avoiding palliative gastrectomy and being content with a simple repair if an R0 resection cannot be performed in the initial surgery, suggesting that neoadjuvant therapy administered after initial surgery may make an R0 resection possible in a second surgery (13). In contrast to their suggestions, three patients in the present study sustained perforation during neoadjuvant therapy, indicating that neoadjuvant therapy itself carries a risk of perforation. The authors of the present manuscript believe that utmost attention must be paid to patients who are refractory to neoadjuvant therapy. Bernardi et al. added hyperthermic intraperitoneal chemotherapy (HIPEC) to the two-stage treatment approach, and performed a laparoscopic total gastrectomy and administered HIPEC after a laparoscopic abscess drainage and primary repair (14). They stated that HIPEC has a favorable effect on treatment. The results of their study reporting on only one patient must be supported with studies involving larger series of patients.

Patients with a poor general condition who have never undergone a gastrectomy due to tumor-related factors constitute another group of patients. Surgeons are often content with a primary repair with an omental patch in such patients, although the worst outcomes in literature have been reported in patients undergoing primary repair (10). It is considered that these patients have leakage secondary to the difficulties in repairing the inflamed tissues involved by the tumor (2). That said, the high mortality in such patients may be attributed to the fact that a primary repair is often performed in patients with

an unresectable tumor and with a poor general condition that makes them unsuitable for gastrectomy. In literature, the mortality rate associated with perforations repaired with a simple closure technique ranges from 12.5–100% (15), and the present study also reports a high mortality rate, similar to those reported in literature, with six out of the 11 patients (54.5%) who were treated with a primary repair died during their stay in hospital. Roviello et al. reported on four patients with PGC who were treated with a local repair and who died after surgery, and one patient who died 5.2 months after surgery for the primary disease (6). The high rate of non-resection surgeries other than local repairs in the present study was attributed to the poor general medical condition of the patients, and the difficulties faced in resecting the malignant tissues due to the advanced stage of the disease.

Serosal invasion and lymph node metastasis are used in the staging of tumors, with their presence indicating an advanced disease stage. Perforation is also considered to be a finding of advanced stage gastric cancer (6,16), although contrary to common belief, perforation can occur also in the early stages of gastric cancer (17). In a study involving 155 patients with PGC, Adachi et al. (3) reported 27 patients with stage I (19%), 16 patients with stage II (12%), 42 patients with stage III (30%) and 55 patients with stage IV (39%) disease. In the present study, only one patient had stage II disease, whereas six patients had stage III (18%) and 23 patients (77%) had stage IV disease.

There is a common concern that malignant cells are also released into the abdominal cavity along with the gastric content from the perforation site (3,9). It is considered that the dissemination of malignant cells results in peritoneal implantation and early tumor recurrence. However, the 5-year survival rate in the reported series of patients with PGC is comparable to that in patients with gastric cancer, but without perforation (3,9,11). This finding suggests that the possible peritoneal dissemination associated with perforation in patients undergoing gastrectomy does not affect survival (2,11,16).

In their study, Gretsch et al. identified the risk score (indicating the general condition of the patients) as the only parameter affecting 30-day mortality [10], while other studies have reported symptom duration, perioperative shock and similar complications as important factors affecting in-hospital mortality (10,11,18). The present study found that the presence of perioperative sepsis correlates with in-hospital mortality. There was a significant difference between septic and non-septic patients in terms of mortality rates ($p<0.01$)

The in-hospital mortality rate in the present study was 33.3%, which is considerably higher than those reported in literature. The authors consider that the main reason for the high mortality rate in the present study was the simple repair of the perforation that had to be performed in most patients due to a poor perioperative general condition, and most patients having advanced stage tumors.

In conclusion, patients with PGC represent a challenge to surgeons due to difficulties encountered in treatment and the poor prognosis in this patient group. A surgeon should not abstain from gastrectomy in eligible patients. Primary repair must be performed when the general condition of the patient and tumor-related factors make a gastrectomy impossible. However, a gastrectomy should be planned afterwards after correcting the unfavorable conditions. It must be kept in mind that appropriate surgical treatment and the successful management of sepsis are of vital importance in patients with PGC.

References

1. Hata T, Sakata N, Kudoh K, Shibata C, Unno M. The best surgical approach for perforated gastric cancer: One-stage vs. two-stage gastrectomy. Gastric Cancer 2014; 17: 578-587.
2. Ozmen MM, Zulfikaroglu B, Kece C, Aslar AK, Ozalp N, Koc M. Factors influencing mortality in spontaneous gastric tumour perforations. J Int Med Res 2002; 30: 180-184.
3. Adachi Y, Aramaki M, Shiraishi N, Shimoda K, Yasuda K, Kitano S. Long-term survival after perforation of advanced gastric cancer: Case report and review of the literature. Gastric Cancer 1998; 1: 80-83.
4. Kandel BP, Singh Y, Singh KP, Khakurel M. Gastric cancer perforation: Experience from a tertiary care hospital. JNMA J Nepal Med Assoc 2013; 52: 489-493.
5. Kotan C, Sumer A, Baser M, Kiziltan R, Carparlar MA. An analysis of 13 patients with perforated gastric carcinoma: A surgeon's nightmare? World J Emerg Surg 2008; 3: 17.
6. Roviello F, Rossi S, Marrelli D, De Manzoni G, Pedrazzani C, Morgagni P, et al. Perforated gastric carcinoma: a report of 10 cases and review of the literature. World J Surg Oncol 2006; 4: 19.
7. Ergul E, Gozetlik EO. Emergency spontaneous gastric perforations: Ulcus versus cancer. Langenbecks Arch Surg 2009; 394: 643-646.

8. Mahar AL, Brar SS, Coburn NG, Law C, Helyer LK. Surgical management of gastric perforation in the setting of gastric cancer. Gastric Cancer 2012; 15: 146-152.
9. Lehnert T, Buhl K, Dueck M, Hinz U, Herfarth C: Two-staged radical gastrectomy for perforated gastric cancer. Eur J Surg Oncol 2000; 26: 780-784.
10. Gertsch P, Yip SK, Chow LW, Lauder IJ. Free perforation of gastric carcinoma. Results of surgical treatment. Arch Surg 1995; 130: 177-181.
11. Kasakura Y, Ajani JA, Fujii M, Mochizuki F, Takayama T. Management of perforated gastric carcinoma: a report of 16 cases and review of world literature. Am Surg 2002; 68: 434-440.
12. Shih CH, Yu MC, Chao TC, Huang TL, Jan YY, Chen MF. Outcome of perforated gastric cancer: twenty years experience of one institute. Hepatogastroenterology 2010; 57: 1320-1324.
13. Xiong W, Wang W, Wan J. [Surgical strategy of diagnosis and treatment for acute perforated gastric cancer]. Zhonghua Wei Chang Wai Ke Za Zhi 2018; 21: 1218-1222.
14. Bernardi D, Asti E, Ferrari D, Bonavina L. Drainage of a Subphrenic Abscess Followed by Two-Stage Gastrectomy and Adjuvant Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for Perforated Gastric Carcinoma: A Case Report. Am J Case Rep 2018; 19: 1113-1116.
15. Soybel DI. Gastric outlet obstruction, perforation and other complications of gastroduodenal ulcer. In: Wolfe MM, editor. Therapy of digestive disease disorders: a companion to Sleisenger and Fordtran's gastrointestinal and liver disease. Philadelphia: WB Saunders Company 2000; 153.
16. Lee HJ, Park DJ, Yang HK, Lee KU, Choe KJ: Outcome after emergency surgery in gastric cancer patients with free perforation or severe bleeding. Dig Surg 2006; 23: 217-223.
17. Kitakado Y, Tanigawa N, Muraoka R. A case report perforated early gastric cancer. Nippon Geka Hokan 1997; 66: 86-90.
18. Chow LW, Yuen ST, Chau KY, Lauder IJ: Long term survival after gastrectomy for advanced bleeding or perforated gastric carcinoma. Eur J Surg 1996; 162: 723-727.