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Original Article

Treatment Modality Based Survival in Gastric Carcinoma Patients with Stand-Alone Peritoneal Metastasis: a Case-Control Study

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

ABSTRACT

Purpose: To date, there are no promising treatments for gastric carcinoma with peritoneal metastasis. Some researchers have suggested a survival benefit of gastrectomy in select patients. This study investigated the survival of gastric carcinoma patients with stand-alone peritoneal metastasis according to the type of treatment modality.
Materials and Methods: We reviewed the data of 132 patients with gastric carcinoma and stand-alone peritoneal metastasis. We performed gastrectomy when the primary tumor was deemed resectable and systemic chemotherapy was administered. We analyzed patient survival according to the type of treatment, and the prognostic value of gastrectomy was evaluated in univariate and multivariate models.
Results: Among all patients, 70 underwent gastrectomy plus chemotherapy, 20 underwent gastrectomy alone, 36 underwent chemotherapy alone, and 6 received supportive care. The median patient survival was 13 months. Patients who underwent gastrectomy had significantly longer survival than those who did not undergo gastrectomy (14 vs. 8 months, P<0.001). Patients who received chemotherapy showed significantly longer survival than those who did not (13 vs. 7 months, P=0.032). Patients who underwent gastrectomy plus chemotherapy showed better survival than those who underwent other treatments. In multivariate analysis, gastrectomy was found to be an independent prognostic factor (hazard ratio, 0.52; 95% confidence interval, 0.33–0.82) in addition to chemotherapy.
Conclusions: Our study showed that patients who underwent gastrectomy plus chemotherapy had the best survival. Although the survival benefit of gastrectomy remains uncertain, it is a favorable prognostic indicator in patients with stand-alone peritoneal metastasis.

Keywords: Stomach neoplasm; Peritoneal metastasis; Gastrectomy

INTRODUCTION

Despite the decrease in global incidence, gastric carcinoma is the fifth most common cancer and the third leading cause of cancer-related death worldwide [1]. With advances in the treatment of gastric carcinoma, there are various multidisciplinary treatment options available such as minimally invasive surgery, endoscopic treatment, molecular targeting agents, and immunotherapy [2,3]. Curative surgery, including gastric resection and regional

jgc Journal of Gastric Cancer

lymph node dissection, remains the mainstay of treatment for gastric carcinoma. Patients with early stage disease have a ≥90% survival rate after surgery alone [4]. However, systemic chemotherapy is the only treatment option for metastatic gastric carcinoma, and the prognosis is dismal, with a median survival of 11–13 months [5].

Peritoneal metastasis is the most common form of metastasis in gastric carcinoma. The post chemotherapy median survival of gastric carcinoma patients with peritoneal metastasis is approximately 10 months [6]. Some researchers have reported an improvement in patient survival with extensive peritonectomy combined with hyperthermic intraperitoneal chemotherapy [7,8]. However, this treatment has not been widely accepted due to high morbidity and mortality. Recently, a conversion surgery that combined induction chemotherapy and a second surgery was introduced as a new treatment modality for patients with peritoneal metastasis. Some studies reported a good response in peritoneal metastasis and an improvement in the curative resection rate through systemic [9] or intraperitoneal induction chemotherapy [10].

The survival benefit of gastrectomy for gastric carcinoma with peritoneal metastasis is controversial. Some researchers have reported improved survival with gastrectomy in patients with peritoneal metastasis [11]. However, other studies reported no significant benefit of gastrectomy [12,13]. In a large randomized controlled trial (RCT; REGATTA trial), gastrectomy did not improve survival compared to chemotherapy alone in metastatic gastric carcinoma [14]. However, this study included a heterogeneous population with various types of metastases, and the effect of gastrectomy could not be assessed in patients with peritoneal metastasis alone. In our institution, we performed palliative gastrectomy when the primary tumor was deemed resectable and administered systemic chemotherapy for stand-alone peritoneal metastasis. In this study, we aimed to analyze patient survival according to the type of treatment administered and investigated the prognostic value of gastrectomy in gastric carcinoma with stand-alone peritoneal metastasis.

MATERIALS AND METHODS

Patients

Using the data available in our gastric cancer database, we identified 3,617 patients who underwent surgery for gastric carcinoma between and 2009–2013 at our institution (Chonnam National University Hwasun Hospital [CNUHH], Hwasun, Korea). After excluding 124 patients for the presence of other malignancies (n=31), recurrent gastric cancer (n=42), or incomplete data in the database (n=51), we retrospectively reviewed the data of 3,493 patients who underwent surgery for primary gastric carcinoma. The inclusion criterion was the presence of peritoneal metastases alone. We enrolled 132 patients who met this criterion (**Fig. 1**). In our institution, we performed palliative gastrectomy when the primary tumor was deemed surgically resectable, and systemic chemotherapy was administered to these patients. After surgery, the decision of chemotherapy was made at the discretion of the oncologists, depending on the patient's condition. Patients with a poor general condition who were unfit for subsequent chemotherapy received conservative care only. Therefore, we divided patients into the following 4 groups according to the type of treatment: 1) gastrectomy plus chemotherapy, 2) gastrectomy alone, 3) chemotherapy alone, and 4) supportive care only. We investigated the patient survival according to treatment received.

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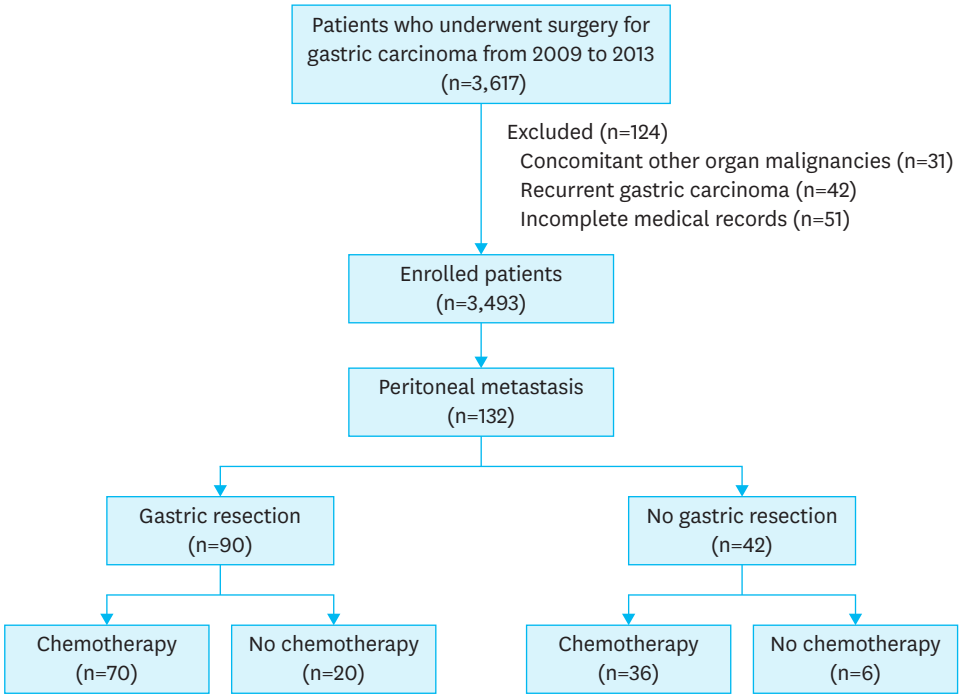

Fig. 1. Flowchart of the patient selection process.

Patients underwent preoperative staging using endoscopy with biopsy and multidetector computed tomography (CT). Other imaging modalities such as chest CT, liver magnetic resonance imaging, or positron emission tomography-CT scanning were used as appropriate. According to predefined diagnostic criteria, we made a clinical diagnosis of tumor invasion and lymph node metastasis [15]. After the surgery, the patients received fluoropyrimidine-based (5-FU, S-1, or capecitabine) and platinum-based (cisplatin or oxaliplatin) chemotherapy with or without trastuzumab. This study was performed after obtaining approval from the Institutional Review Board at CNUHH (CNUHH-2020-166), which waived the requirement for informed consent from patients.

Data collection and definitions

Patient clinical and pathological data were retrieved from a prospectively constructed gastric cancer database. We collected data on the following variables: demographics (age, sex, body mass index [BMI], comorbidities, medical history, nutritional status, and physiologic status), preoperative examination (clinical tumor stage, tumor markers, and other laboratory findings), operative results (gastric resection, reconstruction, lymph node dissection, combined resection, operating time, and operative bleeding), pathologic results (histologic classification, tumor location, tumor size, and pathological stage), and postoperative outcomes (diet start, hospital stay, morbidity, and mortality).

The pathologic tumor stage was based on the eighth edition of the American Joint Committee on Cancer tumor-node-metastasis classification of gastric carcinoma [16]. Postoperative morbidity and mortality were defined as complications or deaths within 30 postoperative days. Postoperative complications were classified as local or systemic according to the site of development. The severity of complications was graded according to the Clavien-Dindo classification of surgical complications [17].

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The primary outcome of this study was overall survival. Overall survival was defined as the time from surgery to death from any cause. To calculate survival status, the patients were followed up until December 2017. Survival data were obtained from the National Cancer Registry and medical records. The median follow-up period was 13 months (range, 1–94 months).

Statistical analysis

Data were expressed as mean±standard deviation or number (%). Student's t-test was used for continuous variables, and the χ^2 test or Fisher's exact test was used for categorical variables. The Kaplan-Meier method and log-rank test were used for the survival analysis. The Cox proportional hazards model was used for multivariate analysis of prognostic factors. Statistical analysis was performed using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, USA). Two-sided P-values of <0.05 were considered statistically significant.

RESULTS

The clinicopathological characteristics of the patients are shown in **Table 1.** There were 84 male and 48 female patients, with a mean age of 59.6±14.9 years. Gastrectomy was

Table 1. Patient characteristics

Variables	Patients (n=132)
Age (yr)	59.6±14.9
Sex	
Male	84 (63.6)
Female	48 (36.4)
Body mass index (kg/m²)	21.6±3.3
Comorbidity	71 (53.8)
ASA status	
1	48 (36.4)
2	73 (55.3)
3	11 (8.3)
Tumor location	
Lower	52 (39.4)
Middle	31 (23.5)
Upper	23 (17.4)
Whole stomach	26 (19.7)
Clinical T stage	
cT2	8 (6.1)
cT3	26 (19.7)
cT4a	78 (59.1)
cT4b	20 (15.2)
Clinical N stage	
cN0	23 (17.4)
cN1	37 (28.0)
cN2	35 (26.5)
cN3	37 (28.0)
Operation	
Distal gastrectomy	42 (31.8)
Total gastrectomy	48 (36.4)
No resection	42 (31.8)
Combined organ resection	31 (23.5)
Treatment modalities	
Gastrectomy plus chemotherapy	70 (53.0)
Gastrectomy alone	20 (15.2)
Chemotherapy alone	36 (27.3)
Supportive care	6 (4.5)

Data are shown as mean±standard deviation or number (%).
ASA = American Society of Anesthesiologists physiologic status.

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performed in 90 (68.2%) patients, including distal (n=42) and total gastrectomy (n=48). Combined organ resection was performed in 31 patients (23.5%). Chemotherapy was administered to 106 patients (80.3%). Overall, 70 (53.0%) patients underwent gastrectomy plus chemotherapy, 20 (15.2%) patients underwent gastrectomy alone, 36 (27.3%) patients received chemotherapy alone, and 6 (4.5%) patients received supportive care only.

Short-term outcomes of gastrectomy in peritoneal metastasis

Table 2 shows the data of short-term surgical outcomes in 90 patients who underwent non-curative gastrectomy for peritoneal metastasis compared with patients who underwent conventional curative gastrectomy (n=3,344). The mean age of patients with conventional curative gastrectomy was 61.3±11.9 years, and the mean BMI was 23.6±3.2 kg/m^2. Of all the patients undergoing curative gastrectomy, 57.8% (n=1,933) had comorbidities. Distal and total gastrectomy was performed in 2020 (81.3%) and 603 (18.0%) patients, respectively. Compared with the non-curative gastrectomy group, the curative gastrectomy group showed a significantly higher BMI (23.6% vs. 21.5%, P<0.001) and lower frequency of total gastrectomy (18.0% vs. 53.3%, P<0.001).

The incidence of local complications was higher after non-curative gastrectomy (23.3% vs. 13.8%, P=0.014). However, only paralytic ileus showed a significantly higher incidence among local complications, while other complications were similar. The incidence of grade ≥3 complications or mortality did not significantly differ between the 2 groups, neither did the postoperative length of hospital stay.

Survival according to treatment

During follow-up, 128 of 132 patients died. The median overall survival in all patients was 13 months (95% confidence interval [CI], 11.5–14.5). The 1-year-and 2-year survival rates were 52% and 16%, respectively.

Fig. 2 shows the Kaplan-Meier survival curves according to the type of treatment. With regard to gastrectomy, patients who underwent gastrectomy showed significantly longer survival than those without gastrectomy. The median survival rates of patients with and without

Table 2. Short-term surgical outcomes

Variables	Gastrectomy in peritoneal metastasis (n=90)	Curative gastrectomy (n=3,344)	P-value
Overall morbidity	22 (24.4)	530 (15.8)	0.028
Systemic complications	4 (4.4)	119 (3.6)	0.563
Local complications	21 (23.3)	461 (13.8)	0.014
Mortality	0	19 (0.6)	1.000
≥Grade 3 complications	5 (5.6)	112 (3.3)	0.233
Diet start (POD)	2.9±1.7	2.7±2.4	0.259
Postoperative fever	18 (20.0)	525 (15.7)	0.270
Hospital stay (POD)	9.8±5.1	9.0±6.5	0.224
Major complications			
Abdominal infection	2 (2.2)	70 (2.1)	0.773
Abdominal bleeding	2 (2.2)	46 (1.4)	0.826
Anastomosis leak	1 (1.1)	24 (0.7)	0.845
Paralytic ileus	9 (10.1)	53 (1.6)	<0.001
Luminal bleeding	3 (3.3)	79 (2.4)	0.806
Ascites	1 (1.1)	54 (1.6)	0.964
Pancreatic fistula	2 (2.2)	21 (0.6)	0.524
Wound	0	33 (1.0)	0.689

Data are presented as mean±standard deviation or number (%).
POD = postoperative day.

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gastrectomy were 14 and 8 months, respectively (log-rank P<0.001) (**Fig. 2A**). Patients who received chemotherapy also showed significantly longer survival than those who did not (**Fig. 2B**). The median survival rates of patients with and without chemotherapy were 13 and 7 months, respectively (log-rank P=0.032). When survival rates were compared among groups with different treatment modalities, patients who underwent gastrectomy plus chemotherapy showed better survival (median survival, 15 months; 95% CI, 12.5–17.5) than those who underwent gastrectomy or chemotherapy alone (**Fig. 3**).

Univariate and multivariate analyses of prognostic factors

To determine the prognostic factors, we examined patient survival according to demographic factors (age, sex, malnutrition, and comorbidity), tumor factors (clinical T and N stage, ascites, serum carcinoembryonic antigen, and carbohydrate antigen 19-9 level), and

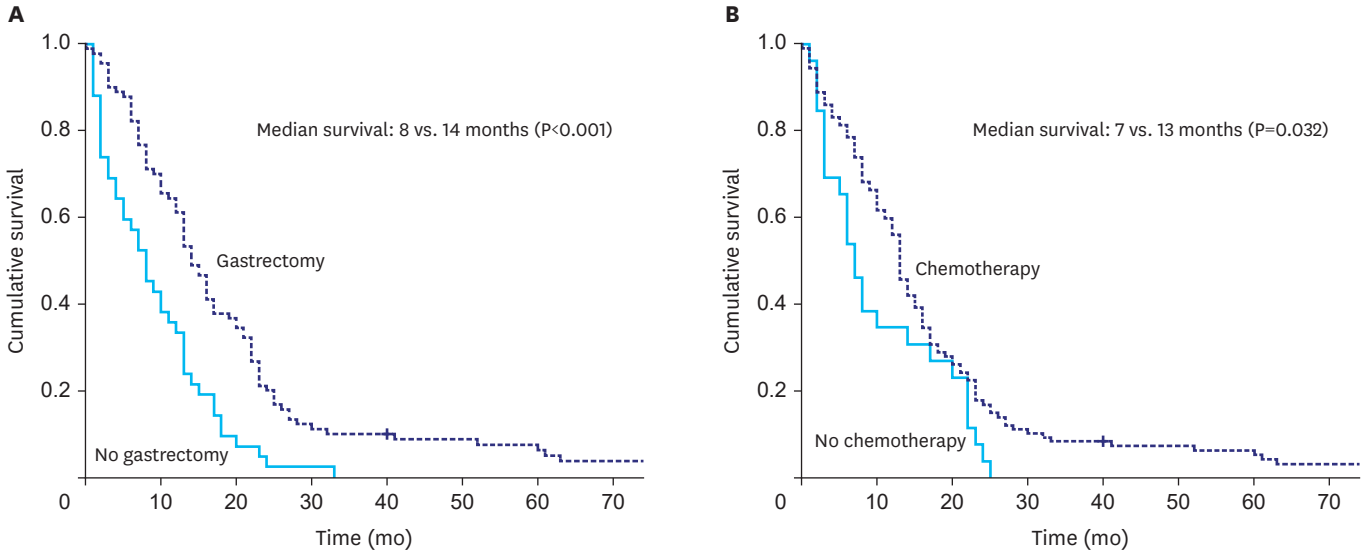

Fig. 2. Kaplan-Meier survival curves for gastrectomy (A) and chemotherapy (B). Patients with gastrectomy had significantly longer survival than those without (median, 14 vs. 8 months, P<0.001). Patients with chemotherapy had significantly longer survival than those without (13 vs. 7 months, P=0.032).

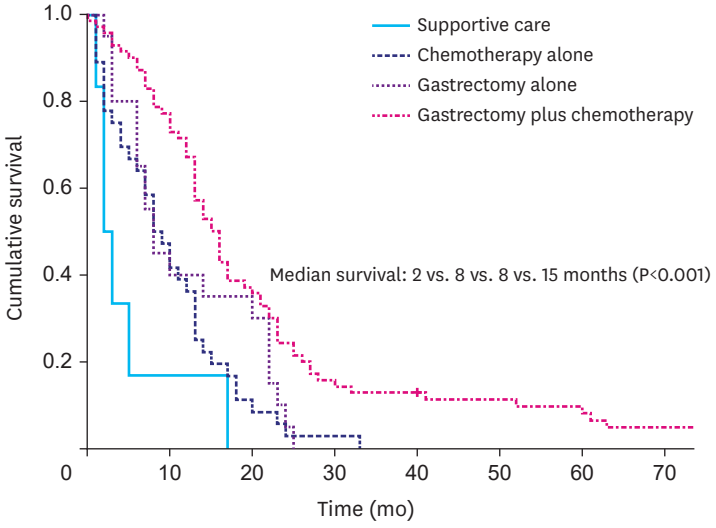

Fig. 3. Survival curves according to treatment modalities. Gastrectomy plus chemotherapy showed better survival than gastrectomy or chemotherapy alone.

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Table 3. Results of univariate and multivariate analyses of prognostic factors

Variables	Univariate			Multivariate		
	HR	95% CI	P-value	HR	95% CI	P-value
Demographic factors						
Age (≥70 yr)	1.17	0.81–1.69	0.409			
Sex (male)	0.77	0.54–1.11	0.164			
Malnutrition	1.00	0.61–1.63	1.000			
Comorbidity	1.16	0.82–1.64	0.407			
Tumor factors						
cT (cT4ab)*	1.43	0.96–2.13	0.008	1.03	0.64–1.63	0.910
cN (cN3)*	1.63	1.11–2.41	0.014	1.53	1.03–2.29	0.036
Ascites	1.76	1.24–2.52	0.002	1.37	0.93–2.02	0.107
CEA (elevation)	1.06	0.71–1.57	0.769			
CA 19-9 (elevation)	0.96	0.63–1.45	0.847			
Treatment factors						
Gastrectomy	0.46	0.32–0.68	<0.001	0.52	0.33–0.82	0.005
Chemotherapy	0.63	0.40–0.97	0.036	0.53	0.34–0.84	0.006

HR = hazard ratio; CI = confidence interval; CEA = carcinoembryonic antigen; CA 19-9 = carbohydrate antigen 19-9.
*Clinical tumor stage assessed according to findings shown on computed tomography scan.

treatment factors (gastrectomy and chemotherapy) (**Table 3**). None of the demographic factors was associated with survival. Among the tumor factors, clinical T stage (P=0.009), clinical N stage (P=0.002), and the presence of ascites (P=0.001) were significantly associated with survival. Among the treatment factors, gastrectomy (P<0.001) and chemotherapy (P=0.036) significantly improved patient survival. Multivariate analysis of these factors revealed that clinical N stage (cN0-2 vs. cN3; hazard ratio [HR], 1.53; 95% CI, 1.03–2.29), gastrectomy (HR, 0.52; 95% CI, 0.33–0.82), and chemotherapy (HR, 0.53; 95% CI, 0.34–0.84) were independent prognostic factors in gastric carcinoma with peritoneal metastasis.

DISCUSSION

The survival benefit of gastrectomy for gastric carcinoma with peritoneal metastasis remains uncertain. In this study, we investigated the long-term survival of gastric carcinoma with stand-alone peritoneal metastasis according to the type of treatment received. We found that patients who underwent gastrectomy followed by chemotherapy showed better survival than those who underwent other treatments. Furthermore, gastrectomy is an independent prognostic factor in these patients. The survival benefit of gastrectomy for stand-alone peritoneal metastasis in gastric carcinoma requires extensive validation. However, our results indicate that gastrectomy is a favorable factor for predicting longer survival in gastric carcinoma with stand-alone peritoneal metastasis.

Several studies have investigated the survival benefits of gastrectomy in gastric carcinoma with peritoneal metastasis. In an analysis of 747 patients with peritoneal metastasis, patients showed significantly longer survival after gastrectomy, and gastrectomy was an independent prognostic factor in multivariate analysis [18]. Similarly, Geng et al [19]. and Yang et al [20]. showed that gastrectomy significantly improved the survival of patients with peritoneal metastasis. Li et al [21]. used propensity score matching to analyze 5,640 metastatic gastric cancer patients identified from the Surveillance, Epidemiology, and End Results registry. The authors found that gastrectomy was associated with improved survival in patients who had a single metastasis only.

However, some studies have reported contrasting results. Tokunaga et al [12]. reported that chemotherapy improved survival in patients with peritoneal metastasis, but gastrectomy

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did not. Similarly, Chen et al. [13] showed that gastrectomy improved survival in patients with distant lymph node metastasis or liver metastasis, but not in patients with peritoneal metastasis. One RCT investigated the survival benefit of gastrectomy in patients with metastatic gastric carcinoma [14]. This study failed to demonstrate the survival benefit of gastrectomy plus chemotherapy compared to that of chemotherapy alone. However, this study included various types of metastases, and the survival benefit of gastrectomy for stand-alone peritoneal metastasis could not be adequately assessed. Therefore, further investigations are needed to determine the survival benefit of gastrectomy in patients with peritoneal metastasis alone.

Many studies have suggested that the extent of peritoneal metastasis is a major determinant of survival in patients undergoing gastrectomy for peritoneal metastasis. Hioki et al. [22] analyzed prognostic factors in 101 patients who underwent gastrectomy for peritoneal metastasis. The authors showed that there was a significant difference in survival depending on the extent of peritoneal metastasis. Similarly, Gretschel et al. [23] reported that gastrectomy improved survival when patients had only a few peritoneal metastases to the adjacent peritoneum. Similar results were reported in many other studies, suggesting the survival benefit of gastrectomy in patients with a minimum extent of peritoneal metastasis [18-20], indicating that the decision for gastrectomy needs to be guided by the degree of peritoneal metastasis.

Systemic chemotherapy is the mainstay of treatment for metastatic gastric carcinoma. Theoretically, gastrectomy reduces tumor volume, which, in turn, can increase chemotherapy efficacy and provide immunologic benefits by reducing tumor-associated cytokines and immunosuppression [24]. Therefore, gastrectomy is expected to exert a synergic effect when combined with subsequent chemotherapy in metastatic gastric carcinoma. Nie et al. [18] demonstrated improvement in survival with gastrectomy combined with chemotherapy, but not with gastrectomy alone. Furthermore, gastrectomy significantly improved survival in a subgroup of patients undergoing chemotherapy. Geng et al. [19] reported that patients who underwent gastrectomy plus chemotherapy showed better survival than those who underwent either gastrectomy or chemotherapy alone. Our study showed that patients who underwent gastrectomy combined with chemotherapy showed better survival (median, 15 months) than those who underwent other treatments.

Despite the possible synergic effect of gastrectomy with chemotherapy, it is also concerning that gastrectomy may negatively affect compliance with subsequent chemotherapy. In the REGATTA trial, the gastrectomy group received fewer chemotherapy cycles than the chemotherapy alone group, especially in patients undergoing total gastrectomy [11]. This impaired chemotherapy compliance was thought to be responsible for poor survival in this patient group. Our study showed that compliance with chemotherapy was not significantly affected by gastrectomy, as indicated by 78% in the gastrectomy group and 85% in the no gastrectomy group (P=0.342). The impact of gastrectomy on compliance with subsequent chemotherapy may require further investigation. However, we observed that most patients who underwent gastrectomy underwent subsequent chemotherapy without significant debilitation.

This study had some limitations. First, selection bias was inevitable because of the retrospective nature of this study. Therefore, better survival with gastrectomy may be associated with a relatively better performance status or less tumor burden in patients undergoing gastrectomy. Although our study demonstrated gastrectomy as an independent

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prognostic factor, the survival benefit of gastrectomy may require extensive investigation. Second, we could not assess patient survival after gastrectomy according to the extent of peritoneal metastasis. This may be helpful in defining the indication and guidelines for gastrectomy in cases with stand-alone peritoneal metastasis. Third, this study included only patients who underwent surgery for peritoneal metastasis, which may limit the generalizability of the study results. Finally, patients with missing data were excluded from the present study. However, the number of patients missing data was relatively low because of the prospectively maintained database.

In conclusion, the present study showed that gastrectomy combined with chemotherapy resulted in the best survival in gastric carcinoma with stand-alone peritoneal metastasis. We found that gastrectomy was an independent favorable prognostic factor in addition to chemotherapy. However, the survival benefit of gastrectomy may require further validation in patients with peritoneal metastasis alone.

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