A real-world evidence of efficacy of palliative gastrectomy plus chemotherapy in metastatic gastric cancer patients

Introduction

Gastric cancer (GC) is the fifth most common malignancy and the third leading cause of cancer-related death worldwide. In China, GC ranks second in tumor incidence and mortality. In contrast to other East-Asian countries, early detection of GC is infrequent in the Chinese population, thus over 80% of patients with GC are diagnosed at an advanced stage with poor overall survival (OS). Consequently, it is crucial to provide an improved and optimized treatment strategy that can increase the survival of patients with metastatic gastric cancer (mGC).

Current guidelines generally recommend chemotherapy for patients with mGC, and chemotherapy combined with trastuzumab for those whose cancer is human epidermal growth factor receptor 2 (HER2) positive. The benefit of palliative gastrectomy for patients with metastatic gastric cancer (mGC) is controversial, and suitable candidates for surgery and treatment strategies remain unclear. The present study aimed to investigate the efficacy of palliative gastrectomy plus chemotherapy among patients with mGC and to identify the potential patients for such treatment using real-world data.

Background: The benefit of palliative gastrectomy for patients with metastatic gastric cancer (mGC) is controversial, and suitable candidates for surgery and treatment strategies remain unclear. The present study aimed to investigate the efficacy of palliative gastrectomy plus chemotherapy among patients with mGC and to identify the potential patients for such treatment using real-world data.

Methods: A dataset of 236 patients with mGC diagnosed at the Sun Yat-Sen University Cancer Center from January 1, 2006 to December 31, 2012 were analyzed retrospectively. The cohort comprised 80 patients who had palliative gastrectomy plus chemotherapy (SC) and 156 patients who had chemotherapy only (CO). Propensity score matching (PSM) was employed to minimize the influence of confounders.

Results: The median overall survival of the SC group was significantly better than that of the CO group (Before PSM: 17.0 months vs 12.0 months, P=0.038; after PSM: 17.0 months vs 13.0 months, P=0.017). In the multivariable analysis, SC (Before PSM: hazard ratio (HR) =0.68, P=0.023; after PSM: HR =0.64, P=0.021) was favored for better survival after adjustment for sex, age, year of diagnosis, primary tumor location, and tumor grade. Total gastrectomy (P=0.026) was associated with worse survival for the SC group. The significant survival advantage of SC over CO was retained in patients with single organ metastasis (P=0.016), peritoneal seedings (P=0.039), and those receiving taxane-based chemotherapy (P=0.011).

Conclusion: SC could improve the overall survival of patients with mGC as compared with CO. The chemotherapy regimen and type of resection were proven to influence efficacy. Patients who received taxane-based regimens might be suitable for palliative gastrectomy.

Keywords: first-line chemotherapy, metastatic gastric cancer, palliative gastrectomy, propensity score matching, survival
epidermal growth factor receptor 2 (HER-2) positive. Gastrectomy is recommended to alleviate or control tumor-related complications, such as obstruction and bleeding. However, palliative gastrectomy to reduce the tumor burden or potentially prolong survival remains controversial. The phase 3 randomized controlled trial, REGATTA, has failed to demonstrate a survival benefit of gastrectomy followed by chemotherapy using S-1/cisplatin (SP) compared with chemotherapy alone for advanced GC with a single non-curable factor.9 Although this result seems to settle the discussion on palliative gastrectomy, several questions remain. Notably, patients who underwent palliative gastrectomy demonstrated poorer compliance with chemotherapy than those who had chemotherapy alone, and patients with lower third gastric cancer benefitted more from surgery than those with upper third tumors, implying that the timing of surgery and the type of resection provided might considerably influence survival benefit. Moreover, the chemotherapy used in the REGATTA trial was restricted to the combination of oral S-1 80 mg/m² per day on days 1–21 and cisplatin 60 mg/m² on day 8 of every 5-week cycle, and whether other regimens combined with surgery could be beneficial remains unclear. By contrast, many retrospective studies have challenged the conclusion of the REGATTA trial and have demonstrated improved survival following non-curative gastrectomy, among which one study even observed an increase in the median OS (mOS) of 9.8 months in patients who only had peritoneal seeding and received preoperative palliative chemotherapy.10–18 As such, it remains underdetermined as to whether the survival improvement by palliative gastrectomy is dependent on factors related to the surgical performance or the chemotherapy regimen provided.

Thus, the present study aimed to evaluate the survival benefit of palliative gastrectomy plus chemotherapy compared with chemotherapy alone in patients with mild- or asymptomatic mGC, to investigate the prognostic factors related to clinicopathological and treatment, and to optimize the treatment strategy based on real-world data.

Methods

Ethics statement

All patients provided written informed consent prior to the retrospective data retrieval from medical records. The study was conducted according to the principles expressed in the Declaration of Helsinki.

Patient and data collection

Patients diagnosed with gastric adenocarcinoma with synchronously distant metastasis from January 1st, 2006 to December 31st, 2012 in Sun Yat-Sen University Cancer Center (SYSUCC) were included in the study, and their clinicopathological data and radiographic images were reviewed for selection. Primary gastric tumors were diagnosed by endoscopy or surgical histopathology, and distant metastases were diagnosed by computed tomography or ultrasound imaging (or both), or biopsy histopathology. The palliative gastrectomy should be performed in the first-line treatment; however, the diagnosis-to-surgery interval was not limited for inclusion. The exclusion criteria were as follows: (1) Patients younger than 18 or with an Eastern Cooperative Oncology Group performance status (ECOG PS) ≥2; (2) patients with non-adenocarcinoma histology; (3) patients for whom it was unknown whether gastrectomy had been performed; (4) patients who have had metastasectomy, local ablation, or hyperthermic intraperitoneal chemoperfusion (HIPEC); (5) patients who did not receive palliative chemotherapy; (6) patients who had emergency gastrectomy to treat tumor-related complications; and (7) patients who received radical gastrectomy after successful conversion therapy. The following clinicopathological data were collected: Age; sex; year of diagnosis; primary tumor location; metastatic sites; tumor pathological type and grade; baseline serum carcinoembryonic antigen (CEA); and treatment information, including gastrectomy and its timing, types of resection and results of lymph node examining, first-line chemotherapy regimens, and cycles of usage. Figure 1 shows the process of patient selection. Patients recruited according to the inclusion and exclusion criteria were then sub-grouped as the SC group (patients receiving palliative gastrectomy plus chemotherapy) and the CO group (patients receiving chemotherapy only), based on the treatment received.

Follow-up data were collected from the follow-up records constructed and renewed by the Department of Follow-up of SYSUCC. Patients who were uncontactable or refused to answer inquiries were regarded as censored.

Data processing

CEA was categorized as normal or elevated based on its normal range (0–5.00 ng/mL), as used at our institution. To categorize metastatic lesions, bilateral organ metastases were regarded as one organ involving metastasis;
for example, both ovaries with metastases were counted as one organ. Distant (ie, non-regional) metastatic lymph nodes located in multiple regions were also defined as one organ. Chemotherapy regimens were classified into: (1) Fluoropyrimidine (5-fluorouracil, capecitabine, or S-1) plus platinum (cisplatin or oxaliplatin); (2) taxane-based drugs (ie, regimens including paclitaxel and docetaxel); (3) fluoropyrimidine plus irinotecan; (4) fluoropyrimidine monotherapy; and (5) adriamycin-based drugs (ie, regimens including adriamycin and epirubicin). Types of resection were classified as total gastrectomy and partial gastrectomy, and those lacking clear surgical records for the classification, mainly because the surgery was performed in other hospitals, were referred to as “unknown”.

**Figure 1** Flowchart illustrating the case selection process.

**Abbreviations:** GC, gastric cancer; SYSUCC, Sun Yat- Sen University Cancer Center; ECOG PS, Eastern Cooperative Oncology Group performance status; HIPEC, hyperthermic intraperitoneal chemoperfusion.

**Statistical analysis**

Comparisons of patient characteristics between the SC and CO groups were performed using the chi-squared and Fisher’s exact tests for categorical variables. OS was the primary endpoint of this study, which was defined as the time from the date of histological diagnosis of primary cancer to the date of death or last follow-up. The Kaplan–Meier method, with the log-rank test, were used for survival analysis. Multivariate Cox analysis, involving factors with a P-value <0.100 in the univariate Cox regression analysis, was used to identify independent prognostic factors. Additionally, prognostic factors of the patients in the SC group were investigated. To minimize the effects of confounding factors, the propensity score matching (PSM) method was used to match SC and CO patients in a 1:1
ratio based on the patients’ age, sex, year of diagnosis, primary tumor location, numbers of organs involving metastasis, tumor grade, and baseline CEA. The matching process was conducted using the “MatchIt” R package. The subsequent survival analyses were based on the matched population. Subgroup analyses to evaluate the survival benefit of palliative gastrectomy were performed in patients with particular metastatic lesions and in those receiving different chemotherapy treatments. We carried out the sensitivity analysis based on patients whose OS exceeded 3 months to eliminate possible bias from a relatively poor prognosis (OS <3 months) caused by vicious tumor biological behavior, not the treatment itself. All data analyses were performed using SPSS Statistics 22.0 (IBM Corp., Version 22.0, Armonk, NY, USA) and the “MatchIt” R packages (The R Foundation, version 3.4.2). A two-sided \( P \)-value <0.05 was considered statistically significant.

Results
Patient characteristics
A total of 236 patients were included in the present study. Table 1 summarizes the patient characteristics of the study population. There were 80 patients and 156 patients in the SC and CO groups, respectively. The commonly used first-line chemotherapy regimens were fluoropyrimidine plus platinum and taxane-based regimen for both cohorts; however, only 53.0\% (n=125) of the patients received more than four cycles of first-line chemotherapy. Patients in the SC group tended to be diagnosed in the earlier years, to have well or moderately differentiated tumors, to have cancer in the lower two thirds of the stomach, and to have metastatic lesions in only one organ, compared with the patients in the CO group.

The chemotherapy regimens and the number of agents applied, the route of administration, and the number of treatment cycles were comparable between groups. After being matched using PSM, no significant differences were detected in all the characteristics analyzed, except the proportions of hepatic metastasis and peritoneal metastasis. This implied that patients with hepatic metastasis tended not to receive palliative gastrectomy while those with peritoneal metastasis did. However, given that metastatic lesions could involve more than one organ, there was no clinical significance in obtaining a balanced distribution of metastatic organs.

Survival analysis
The mOS of the SC group was significantly longer than that of the CO group (17.0 months vs 12.0 months, \( P=0.038 \)) (Figure 2A). Palliative gastrectomy also demonstrated significantly prolonged mOS in the matched population (17.0 months vs 13.0 months, \( P=0.017 \)) (Figure 2B). In the multivariate analysis, after adjustment for sex, age at diagnosis, year of diagnosis, primary tumor location, and tumor grade, palliative gastrectomy (hazard ratio (HR) =0.68 [95% confidence interval (CI): 0.49–0.95], \( P=0.023 \); matched HR =0.64 [95% CI: 0.44–0.94], \( P=0.021 \)) was proved to be associated with better survival.

Subgroup analysis of patients with different metastatic sites and chemotherapy regimens
Figure 3 demonstrates the survival benefit of SC as compared to CO in particular subgroups of patients. Among the patients whose metastatic lesions were limited to a single organ, palliative gastrectomy was observed to robustly improve their mOS (HR =0.62 [95% CI, 0.42–0.92], \( P=0.016 \)). In terms of chemotherapy, a prolonged survival advantage was obtained from gastrectomy in patients who received taxane-based chemotherapy (HR =0.52 [95% CI, 0.31–0.86], \( P=0.011 \)) rather than fluoropyrimidine plus platinum (HR =0.76 [95% CI, 0.43–1.33], \( P=0.330 \)).

Surgical factors that favored a prolonged survival among SC patients
The analyses took into consideration variables associated with surgery, including the timing of surgery, the type of resection, the number of lymph nodes examined, and the ratio of positive lymph nodes to total lymph nodes examined, in addition to patient characteristics (Table 2). The type of resection was found to be independently associated with survival (\( P=0.026 \)). Poorer survival was observed in patients who underwent total gastrectomy compared with patients who underwent other types of gastrectomy. Nevertheless, the timing of surgery (before or after chemotherapy started) and the number of retrieved lymph nodes were found to have no significant influence on survival. Moreover, in the univariate Cox analysis, a high ratio (≥0.55) of positive lymph nodes to total lymph nodes examined was significantly associated with poorer survival (\( P=0.024 \)), but was not an independent prognostic factor in the multivariate analysis (\( P=0.076 \)).

Sensitivity analysis
After excluding 45 patients with OS ≤3 months, the efficacy of SC was re-evaluated and similar results
Table 1 Demographic and clinicopathological characteristics of the unmatched and matched population by propensity score matching (PSM)

| Characteristics                  | Number (%) | P-value | Matched cohort P-value |
|----------------------------------|------------|---------|------------------------|
|                                  | All cohort | With palliative gastrectomy | Without palliative gastrectomy |
| Age, years                       |            |         |                        |
| <50                              | 84 (35.6%) | 30 (37.5%) | 54 (34.6%) |
| 50–59                            | 66 (28.0%) | 19 (23.8%) | 47 (30.1%) |
| 60–69                            | 63 (26.7%) | 22 (27.5%) | 41 (26.3%) |
| ≥70                              | 23 (9.7%)  | 9 (11.3%)  | 14 (9.0%)  |
| Sex                              |            |         |                        |
| Male                             | 155 (65.7%)| 56 (70.0%) | 99 (63.5%) |
| Female                           | 81 (34.3%) | 24 (30.0%) | 57 (36.5%) |
| Year of diagnosis                |            |         |                        |
| 2006–2008                        | 52 (22.0%) | 26 (32.5%) | 26 (16.7%) |
| 2009–2010                        | 104 (44.1%)| 34 (42.5%) | 70 (44.9%) |
| 2011–2012                        | 80 (33.9%) | 20 (25.0%) | 60 (38.5%) |
| Primary tumor location           |            |         |                        |
| Upper third                      | 150 (63.6%)| 42 (52.5%) | 108 (69.2%) |
| Middle third                     | 49 (20.8%) | 22 (27.5%) | 27 (17.3%) |
| Lower third                      | 28 (11.9%) | 14 (17.5%) | 14 (9.0%) |
| NOS                              | 9 (3.8%)   | 2 (2.5%)  | 7 (4.5%)   |
| Metastatic site                  |            |         |                        |
| Liver                            | 72 (30.5%) | 13 (16.3%) | 59 (37.8%) |
| Lung                             | 18 (7.6%)  | 3 (3.8%)  | 15 (9.6%)  |
| Ovary                            | 3 (1.3%)   | 1 (1.3%)  | 2 (1.3%)   |
| Peritoneal implantation          | 111 (47.0%)| 47 (58.8%) | 64 (41.0%) |
| Distal lymph node                | 93 (39.4%) | 27 (33.8%) | 66 (42.3%) |
| Number of organs involving metastasis |        |         |                        |
| One                              | 157 (66.5%)| 60 (75.0%) | 97 (62.2%) |
| More than one                    | 79 (33.5%) | 20 (25.0%) | 59 (37.8%) |
| Pathology type                   |            |         |                        |
| Adenocarcinoma, NOS              | 214 (90.7%)| 70 (87.5%) | 144 (92.3%) |
| Mucinous adenocarcinoma          | 6 (2.5%)   | 4 (5.0%)  | 2 (1.3%)   |
| Signet ring cell carcinoma       | 16 (6.8%)  | 6 (7.5%)  | 10 (6.4%)  |
| Tumor Grade                      |            |         |                        |
| G1/G2                            | 108 (45.8%)| 44 (55.0%) | 64 (41.0%) |
| G3/G4                            | 128 (54.2%)| 36 (45.0%) | 92 (59.0%) |
| Baseline CEA                     |            |         |                        |
| Normal range                     | 130 (55.1%)| 48 (60.0%) | 82 (52.6%) |
| High                             | 106 (44.9%)| 32 (40.0%) | 74 (47.4%) |
| Treatment factors                |            |         |                        |
| Chemotherapy regimens            |            |         |                        |
| Fluoropyrimidine plus Platinum   | 95 (40.3%) | 29 (36.3%) | 66 (42.3%) |
| Taxane-based drugs               | 104 (44.1%)| 36 (45.0%) | 68 (43.6%) |
| Fluoropyrimidine plus Irinotecan | 5 (2.1%)   | 1 (1.3%)  | 4 (2.6%)   |

(Continued)
Table 1 (Continued).

| Characteristics                        | Number (%)                      |  | P-value d | Matched cohort P-value |
|----------------------------------------|---------------------------------|---|------------|------------------------|
|                                        | All cohort                      | With palliative gastrectomy | Without palliative gastrectomy |
|                                        |                                 | p-value                       |  |                         |
| Fluoropyrimidine                       | 28 (11.9%)                      | 12 (15.0%)                    | 16 (10.3%)                |                         |
| Adriamycin-based drugs                 | 4 (1.7%)                        | 2 (2.5%)                      | 2 (1.3%)                  |                         |
| Number of chemotherapy agents          |                                 |                               |                           |                         |
| One                                    | 30 (12.7%)                      | 14 (17.5%)                    | 16 (10.3%)                | 0.286                   |
| Two                                    | 187 (79.2%)                     | 60 (75.0%)                    | 127 (81.4%)               | 0.260                   |
| Three                                  | 19 (8.1%)                       | 6 (7.5%)                      | 13 (8.3%)                 |                         |
| Route of medication                   |                                 |                               |                           |                         |
| Oral intake                            | 144 (61.0%)                     | 52 (65.0%)                    | 92 (59.0%)                | 0.369                   |
| Intravenous only                       | 92 (39.0%)                      | 28 (35.0%)                    | 64 (41.0%)                | 0.197                   |
| Cycles of chemotherapy                |                                 |                               |                           |                         |
| ≤4 cycles                              | 111 (47.0%)                     | 32 (40.0%)                    | 79 (50.6%)                | 0.121                   |
| >4 cycles                              | 125 (53.0%)                     | 48 (60.0%)                    | 77 (49.4%)                | 0.425                   |
| Palliative gastrectomy                 |                                 |                               |                           |                         |
| Yes                                    | 80 (33.9%)                      | 80 (100.0%)                   | 0 (0.0%)                  |                         |
| No                                     | 156 (66.1%)                     | 0 (0.0%)                      | 156 (100.0%)              |                         |
| Timing of surgery                      |                                 |                               |                           |                         |
| Surgery followed by chemotherapy      |                                 | 73 (91.3%)                    |                           |                         |
| Median cycles of chemotherapy after surgery (Range) | 5 (1.0–12.0) | | | |
| Chemotherapy followed by surgery       |                                 | 7 (8.8%)                      |                           |                         |
| Median cycles of chemotherapy before surgery (Range) | 4.0 (2.0–6.0) | | | |
| Median cycles of chemotherapy after surgery (Range) | 2.0 (0.0–6.0) | | | |
| Types of resection                     |                                 |                               |                           |                         |
| Total gastrectomy                      | 16 (20.0%)                      | 27 (33.8%)                    | 37 (46.3%)                |                         |
| Partial gastrectomy                    |                                 |                               |                           |                         |
| Unknown                                |                                 |                               |                           |                         |
| Number of lymph nodes retrieved and examined |                            |                               |                           |                         |
| ≤15                                    | 15 (18.8%)                      | 65 (81.3%)                    |                           |                         |
| >15                                    |                                 |                               |                           |                         |
| Number of positive lymph nodes (mean ± SD) |                             | 12.16±9.30                   |                           |                         |
| Ratio of positive lymph nodes to total lymph nodes examined c |                             | 0.54±0.27                    |                           |                         |
| <0.55                                  |                                | 40 (50.0%)                    | 40 (50.0%)                |                         |
| ≥0.55                                  |                                |                               |                           |                         |

Notes: *Primary tumor location was defined by endoscopy or computed tomography (CT) findings. *Metastatic lesion location was defined by CT/ultrasound imaging or intraoperative findings. *The cutoff value for ratios of positive lymph nodes to total lymph nodes examined were determined by X-tile software 3.6.1 (Yale University, New Haven, CT, USA). *P-value for comparison in characteristics between unmatched SC and CO groups.

Abbreviations: CEA, carcinoembryonic antigen; NOS, not otherwise specified.
were obtained. The mOS of the SC group remained significantly longer than that in the CO group (19 months [95% CI, 15.28–22.72] vs 13 months [95% CI, 10.88–15.12], \( P = 0.033 \)). In the multivariate analysis, SC (HR = 0.68 [95% CI, 0.47–0.97], \( P = 0.034 \)) remained the superior regimen, demonstrating more favorable survival.

**Discussion**

In patients with mGC, survival prolongation by palliative gastrectomy is still controversial. In the present study, based on real-world data, we aimed to evaluate the survival benefit of palliative gastrectomy plus chemotherapy compared with chemotherapy alone, to investigate treatment factors that favored better survival, and to develop optimal multi-disciplinary treatment.

The results of the present study were consistent with previous retrospective studies,\(^{11,13–17,20,21}\) in that we demonstrated that patients who received palliative gastrectomy plus chemotherapy had a longer OS as compared with those who received chemotherapy only. A meta-analysis involving 19 non-randomized studies and
Table 2 Results of the univariate and multivariate survival analysis by Cox regression of the patients who received gastrectomy plus chemotherapy (SC)

| Variable                                               | Univariable Cox analysis       |
|--------------------------------------------------------|--------------------------------|
|                                                        | HR (95% CI)                    | P-value |
| **Age, years**                                         |                                |         |
| <50                                                    | Reference                       |         |
| 50−59                                                  | 1.17 (0.58, 2.36)               | 0.527   |
| 60−69                                                  | 1.31 (0.66, 2.61)               |         |
| ≥70                                                    | 1.90 (0.80, 4.49)               |         |
| **Sex**                                                |                                |         |
| Male                                                   | Reference                       |         |
| Female                                                 | 0.77 (0.43, 1.40)               | 0.397   |
| **Year of diagnosis**                                 |                                |         |
| 2006−2008                                              | Reference                       |         |
| 2009−2010                                              | 1.21 (0.65, 2.26)               | 0.615   |
| 2011−2012                                              | 0.87 (0.42, 1.81)               |         |
| **Primary tumor location**                            |                                |         |
| Upper one third                                        | Reference                       |         |
| Middle one third                                       | 0.53 (0.27, 1.06)               | 0.101   |
| Lower one third                                        | 0.89 (0.45, 1.76)               |         |
| NOS                                                    | 3.01 (0.71, 12.86)              |         |
| **Number of organs involving metastasis**              |                                |         |
| One                                                    | Reference                       |         |
| More than one                                          | 1.28 (0.70, 2.35)               | 0.428   |
| **Pathology type**                                    |                                |         |
| Adenocarcinoma, NOS                                   | Reference                       |         |
| Mucinous adenocarcinoma                                | 0.82 (0.29, 2.28)               | 0.890   |
| Signet ring cell carcinoma                             | 1.13 (0.44, 2.86)               |         |
| **Tumor Grade**                                        |                                |         |
| G1/G2                                                  | Reference                       |         |
| G3/G4                                                  | 1.45 (0.84, 2.51)               | 0.188   |
| **CEA**                                                |                                |         |
| Normal range                                           | Reference                       |         |
| High                                                   | 1.32 (0.77, 2.26)               | 0.313   |
| **Surgery timing**                                    |                                |         |
| Surgery first                                          | Reference                       |         |
| Chemotherapy first                                     | 0.80 (0.32, 2.02)               | 0.638   |
| **Resection method**                                  |                                |         |
| Total gastrectomy                                      | Reference                       |         |
| Partial gastrectomy                                    | 0.40 (0.19, 0.85)               | 0.047   |
| Unknown                                                | 0.48 (0.24, 0.97)               |         |
| **Number of lymph nodes retrieved and examined**       |                                |         |
| ≤15                                                    | Reference                       |         |
| >15                                                    | 0.79 (0.41, 1.50)               | 0.465   |
| **Ratio of positive lymph nodes to total lymph nodes examined** |            |         |
| <0.55                                                  | Reference                       |         |
| ≥0.55                                                  | 1.85 (1.08, 3.16)               | 0.024   |

(Continued)
comprising 2,911 patients observed a possible survival benefit of gastrectomy compared with non-surgical strategies for stage IV GC. 17 Other studies analyzed factors that favored the beneficial effects of gastrectomy to narrow down the potential surgical candidates, and to optimize clinical treatment. Hsu et al found that younger age, better preoperative nutritional status, less nodal involvement, and postoperative chemotherapy could independently prolong the survival of patients who received palliative gastrectomy. 20 A previous study from our group showed that patients with GC with peritoneal seeding could benefit from palliative chemotherapy followed by gastrectomy. That study also showed that margin-free gastrectomy and more than four cycles of palliative chemotherapy were independent favorable prognostic factors. 11 In the present study, SC was found to be associated with better survival, and subgroup analyses for patients with single organ metastasis and patients with peritoneal seedings confirmed the survival improvement resulting from palliative gastrectomy.

To the best of our knowledge, this is the first study to investigate the survival benefit of palliative gastrectomy taking treatment factors (including surgical performance and chemotherapy medication) into consideration. The REGATTA trial strictly limited the chemotherapy medication and dosage, thus its external validation for patients receiving various regimens with different self-suitable dosages should be doubted. For this reason, we used real-world data and further carried out subgroup survival analyses stratified by the chemotherapy regimens. The most commonly accepted first-line chemotherapy regimen as the primary recommendation in China is fluoropyrimidine (5-FU or capecitabine or S-1) plus platinum (cisplatin or oxaliplatin). 22-24 Taxane-based regimens are also adopted as first-line chemotherapy; however, a high incidence of intolerance of taxane-based duplexes or triplexes has retarded their clinical application. 25-27 In the subgroup analysis, a survival advantage was derived from gastrectomy in patients receiving taxane-based chemotherapy, whereas patients treated with fluoropyrimidine plus platinum might not gain a survival benefit from gastrectomy. The chemotherapy-regimen-dependent feature may be attributed to the negative conclusion of the REGATTA trial which used SP for postoperative chemotherapy. The present study preliminarily indicated that specific chemotherapy regimens, such as taxane-based chemotherapy, were suitable for combination with palliative gastrectomy; however, further corroborative evidence is required.

For the patients in the SC group, how to maximize benefit from surgery was explored and questions from the REGATTA trial about the timing and types of surgery were also investigated. In the present study, patients who underwent partial gastrectomy had better survival compared with those who underwent total gastrectomy, probably because of better organ function-preservation. 28 The timing of palliative surgery in relation to chemotherapy was not associated with survival according to our analysis. However, several possible advantages of preoperative chemotherapy were reported in previous studies, including the chance of achieving converging purpose for curative resection and better treatment

| Table 2 (Continued). |
|----------------------|
| **Variable**         | **Univariable Cox analysis** | **Multivariable Cox analysis** |
|                      | **HR (95% CI)**              | **Resection method**          |
| **Chemotherapy regimens** |                    |                               |
| Fluoropyrimidine plus Platinum | Reference | Reference |
| Taxane-based drugs | 1.19 (0.65, 2.18) | 0.34 (0.16, 0.73) |
| Fluoropyrimidine plus Irinotecan | Unmeasurable * | 0.43 (0.21, 0.88) |
| Fluoropyrimidine | 2.70 (1.25, 5.82) |                               |
| Adriamycin-based drugs | 1.72 (0.40, 7.48) |                               |
| **Multivariable Cox analysis** |             |                               |
| **Resection method** |             |                               |
| Total gastrectomy | Reference |                               |
| Partial gastrectomy | 0.34 (0.16, 0.73) |                               |
| Unknown | 0.43 (0.21, 0.88) |                               |

Note: *Unmeasurable, because there’s only one patient in the group.

Abbreviations: HR, hazard ratio; CI, confidence interval; NOS, not otherwise specified; CEA, carcinoembryonic antigen.
compliance compared with postoperative chemotherapy.\textsuperscript{29} For the extent of lymphadenectomy, the number of lymph nodes retrieved was not a prognostic factor, which suggested that D2 lymphadenectomy might not be meaningful and necessary in the palliative gastrectomy. Moreover, since patients with better survival had an opportunity to receive additional chemotherapy, cycles of chemotherapy were not included in the survival analysis.

This was a retrospective real-world study; therefore, factors influencing medical decisions on SC or CO as first-line treatment were various and hard to completely control. Thus, several measures were taken to reduce bias. Appropriate inclusion and exclusion criteria were set to maximize the comparability between the groups and to enhance the simulation of the real decision-making situation. For instance, patients’ general conditions are usually demonstrated the safety of palliative gastrectomy,\textsuperscript{15} evaluation of postoperative complications, adverse events caused by chemotherapy, and the quality of life among the patients in the SC group should be performed in our study; the evaluation were limited because of a lack of information. Third, the sample sizes of some subgroups were too small to analyze, and the conclusions drawn from the subgroup analysis need to be validated in future studies with higher evidence levels.

In conclusion, the present study provided real-world evidence that palliative gastrectomy plus chemotherapy could improve survival in patients with mild or asymptomatic mGC compared with chemotherapy alone. Treatment factors, such as chemotherapy regimens and type of resection, might influence the survival benefit of palliative gastrectomy. Patients who received taxane-based regimens might be suitable for palliative gastrectomy.

Availability of data and materials
The key raw data have been deposited into the Research Data Deposit (http://www.researchdata.org.cn), with the Approval Number of RDDA2019001002 and the datasets used in this study are publicly available.

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