Comparison of Clinical Outcomes of Gastrojejunal Bypass and Gastrectomy in Patients With Metastatic Gastric Cancer

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Abstract. *Background/Aim: Surgical therapy for stage IV gastric cancer patients is still debatable. The clinical outcomes were compared between gastrojejunal bypass and gastrectomy for metastatic gastric cancer patients. Patients and Methods: A total of 110 patients with metastatic gastric cancer who underwent surgery were retrospectively analyzed. Twenty-nine patients underwent gastrojejunal bypass (group B) and 81 underwent gastrectomy (group G). Results: There was no significant difference in the 3-year overall survival between Group G patients with partial gastrectomy and total gastrectomy. However, patients in group G had a significantly better prognosis compared to patients in group B ($p=0.01$ and 0.03 , respectively). The prognosis of patients with postoperative chemotherapy was significantly better in group G compared to group B ($p=0.03$), whereas it was not significantly different for the patients without postoperative chemotherapy ($p=0.24$). Conclusion: Gastrectomy in patients with metastatic gastric cancer may improve survival when combined with postoperative chemotherapy.*

Gastric cancer is the fifth most common cancer and the third leading cause of cancer-related mortality worldwide (1). Among gastric cancers, metastatic gastric cancer has an especially poor prognosis. Although the prognosis of stage IV gastric cancer has been recently improved as a result of new chemotherapeutic and molecular-targeting drugs, the median survival in patients with metastatic gastric cancer is only about 10 months (2, 3).

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Chemotherapy is the standard of care for patients with stage IV gastric cancer, as stated in the Japanese treatment guidelines (4), so these patients are not eligible for radical resection. However, patients with stage IV gastric cancer sometimes undergo surgery, including a gastrojejunal bypass or gastrectomy, to relieve cancer-related symptoms, such as tumor bleeding, obstruction, or perforation. Some studies have indicated that palliative gastrectomy not only relieves cancer-related symptoms but also improves the prognosis. However, other studies have demonstrated that the outcomes of surgical resection in stage IV gastric cancer are poor (5-9).

Recently, investigators of the REGATTA trial concluded that gastrectomy followed by chemotherapy did not impart any benefits to overall survival compared to chemotherapy alone in advanced gastric cancer patients with a single non-curative factor (10). However, this study was a well-planned randomized clinical study for patients with or without surgery, and the patients did not have any symptoms, such as a bleeding or poor oral intake. Besides, the indication or significance of gastrojejunal bypass remains unclear, and surgical therapy for metastatic gastric cancer is still debatable.

The aim of this study was to investigate whether gastrojejunal bypass or palliative gastrectomy contributed to the short-term outcomes and prognoses of patients with metastatic gastric cancer.

Patients and Methods

Patients. A total of 110 patients with metastatic gastric cancer who underwent surgery at Kyoto Prefectural University of Medicine between 2004 and 2015 were retrospectively registered in this study. Of 110 patients, 29 patients underwent gastrojejunal bypass (group B) and 81 patients underwent gastrectomy (group G). The clinical data from the medical records and database of our institution were reviewed. Preoperative diagnoses of gastric adenocarcinoma were confirmed by endoscopy followed by biopsy. Metastatic disease was defined from the preoperative findings on computed tomography and positron emission tomography, or from the intraoperative findings. The clinical stage was determined based on the Japanese Classification of Gastric Carcinoma 3rd edition (11). We evaluated

Table I. Comparison of clinicopathological factors.

Variables	n=110	Bypass n=29	Gastrectomy n=81	p-Value ^c
Age, years	67.4±10.7	70.3±7.6	66.4±11.4	0.13
Gender				
Female	38	11 (38%)	27 (33%)	0.66
Male	72	18 (62%)	54 (67%)	
The number of non-curative factor				
1	77	13 (45%)	64 (79%)	<0.001
≥2	33	16 (55%)	17 (21%)	
Preoperative symptoms				
Cancer bleeding	26	8	18	0.56
Stenosis	37	21	16	<0.001
Preoperative poor oral intake				
Presence	43	19 (66%)	24 (30%)	<0.001
Absence	67	10 (34%)	57 (70%)	
Preoperative chemotherapy				
Presence	29	6 (21%)	23 (28%)	0.42
Absence	81	23 (79%)	58 (74%)	
Hb, g/dL	10.9±2.5	10.4±2.6	11.0±2.4	0.25
Alb, g/dL	3.77±0.53	3.58±0.53	3.84±0.05	0.02
CEA, ng/ml	12.1±54.1	6.3±0.8	14.2±63.1	0.13
CA19-9, U/ml	90.9±596.5	15.9±3.06	118.4±696	0.52
cT stage ^a				
T1, 2	13	1 (3%)	12 (15%)	0.10
T3, 4	97	28 (97%)	69 (85%)	
cN stage ^a				
N0, 1	29	9 (31%)	20 (25%)	0.51
N2, 3	81	20 (69%)	61 (75%)	
Location				
ML	67	27 (93%)	40 (49%)	<0.001
U	43	2 (7%)	41 (51%)	
Histological type				
Undifferentiated	75	19 (73%)	56 (69%)	0.70
Differentiated	35	10 (27%)	25 (31%)	
Invasion to other organ				
Presence	35	18 (62%)	17 (21%)	<0.001
Absence	75	11 (38%)	64 (79%)	
Operative Blood loss, ml	329.5±331.8	89.2±177.6	421.2±331.8	<0.001
Operative time, min	239.9±109.3	137.0±41.0	278.6±101.6	<0.001
Postoperative complication ^b				
Presence	22	4 (12%)	18 (22%)	0.33
Absence	88	25 (88%)	63 (78%)	
Grade II		2 (6%)	11 (14%)	
Grade IIIa		2 (6%)	5 (6%)	
Grade IIIb		0 (0%)	1 (1%)	
Grade IVa		0 (0%)	1 (1%)	
Hospital stay, days	25.4±18.7	22.4±21.9	26.5±17.4	0.02
Postoperative chemotherapy				
Presence	83	19 (70%)	64 (79%)	0.15
Absence	27	10 (30%)	17 (21%)	

^aAccording to the Japanese Classification of Gastric Carcinoma 3rd edition; ^bGrade II or above according to the Clavien-Dindo classification; ^cp-Values are from Chi-squared test or Mann-Whitney U-test. Hb: Hemoglobin; Alb: albumin; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen19-9; cT: clinical T; cN: clinical N; ML: middle or lower third of stomach; U: upper third of stomach.

the grade of postoperative complications using the Clavien-Dindo classification. Patients with grade II or greater complications were considered complication-positive (12, 13).

The present study was conducted in accordance with the principles of the Declaration of Helsinki (14), and written informed

consent for the treatments was obtained from all patients. Ethical approval from the Faculty of Science Committee at the Kyoto Prefectural University of Medicine was not required, as the present study was a retrospective observational study without interventions provided for the therapeutic purposes.

Table II. Details of 1st line postoperative chemotherapy.

Chemotherapy regimen	Bypass n=29	Gastrectomy n=81	Total n=110
No chemotherapy	10	17	27
TS-1 based regimen	15	46	61
TS-1 alone	(5)	(19)	(24)
TS-1+CDDP	(7)	(17)	(24)
Others	(3)	(10)	(13)
PTX based regimen	3	9	12
CPT-11 based regimen	1	3	4
Others	0	6	6

TS-1: Tegafur/Gimeracil/Oteracil; CDDP: cis-diamminedichloro-platinum; PTX: paclitaxel; CPT-11: camptothecin-11.

Surgical therapy. In group G, total or subtotal gastrectomy was performed according to the location of the primary tumor. The Billroth I, Roux-en-Y, or esophagogastric anastomosis was performed according to the types of gastrectomy. In group B, the gastrojejunostomy was placed in the middle third of the greater curvature of the stomach using a linear stapler by either a laparoscopic approach or open laparotomy.

Postoperative chemotherapy. The chemotherapeutic regimens were selected based on the judgment of an attending physician and the status of the patient. The main regimens included Tegafur/Gimeracil/Oteracil (TS-1), Paclitaxel, or Camptothecin-11, and were administered according to the standard protocol.

Statistical analysis. The categorical variables in the two groups were compared using the Chi-square test. Continuous variables were summarized by mean ($\pm$ SD), and the groups were compared using the Mann-Whitney *U*-test. Curves for overall survival were derived using the Kaplan-Meier method and were compared using the Log-rank test. A multivariate survival analysis was performed using Cox's proportional hazard regression model. A *p*-value <0.05 was considered significant. JMP 10.0 statistical software for Macintosh (SAS Institute, Cary, NC, USA) was used for all analyses.

Results

Patient characteristics. The clinico-pathological characteristics of the patients are shown in Table I. Multisite distant metastasis, stenosis, and poor preoperative oral intake were significantly frequent in group B. The preoperative serum albumin levels in group B was significantly lower compared to those in group G ($p=0.02$), whereas the preoperative levels of hemoglobin and tumor markers were similar between the two groups. No significant differences were observed regarding clinical T or N stages, histological types, or the frequency of postoperative chemotherapy between the two groups. The location of the primary lesion in the middle and lower thirds of the stomach, and tumor invasion into the surrounding organs were significantly frequent in group B ($p<0.001$).

DG or PG vs. TG : NS
 DG or PG vs. Bypass : $p=0.010$
 TG vs. Bypass : $p=0.026$
 (Log-rank)

Figure 1. Survival analysis according to the type of surgery. Overall survival using the Kaplan-Meier method is shown for patients who underwent total gastrectomy, distal and proximal gastrectomy, or gastrojejunal bypass. DG: Distal gastrectomy; PG: proximal gastrectomy; TG: total gastrectomy.

Complications and postoperative chemotherapy. The grades of complications are shown in Table I. Four patients (12%) in group B, and 18 patients (22%) in group G had postoperative complications of grade 2 or higher ($p=0.33$). Postoperative hospital stays were significantly longer in group G compared to group B [21 days (10-101) versus 15 days (7-117), $p=0.02$].

The details of 1st-line postoperative chemotherapy in both groups are shown in Table II. Nineteen patients (70%) in group B and 64 patients (79%) in group G received any regimens of chemotherapy ($p=0.14$). TS-1-based chemotherapy was frequently given in both groups [15 patients (51%) in group B, and 46 patients (56%) in group G].

Survival analyses. The prognosis was analyzed according to the types of surgery (Figure 1). Although there was no significant difference in the 3-year overall survival (OS) of patients who underwent distal (DG) or proximal (PG) gastrectomy (16.4%) and total gastrectomy (TG) (10.4%) in group G, the patients with either type of gastrectomy showed significantly better 3-year OS compared to the group B patients (4.6%; $p=0.01$ and $p=0.03$, respectively).

Table III shows the correlation between survival and the clinico-pathological factors for the 110 patients. Older age (≥ 70 years, $p=0.004$), presence of poor preoperative oral intake ($p=0.01$), tumor invasion into other organs ($p=0.01$), clinical N2-3 ($p=0.03$), absence of postoperative chemotherapy

Table III. Univariate and multivariate analyses of prognostic factors.

Variables	Univariate			Multivariate		
	n=110	3-years OS (%)	p-Value ^c	HR	95%CI	p-Value ^d
Age, years						
≥70	51	5.43	0.004	1.93	1.15-3.22	0.01
<70	59	14.7				
Gender						
Female	38	8.69	0.98			
Male	72	11.6				
Location						
ML	67	10.7	0.88			
U	43	10.5				
Preoperative poor oral intake						
Presence	43	6.03	0.01	1.17	0.69-1.95	0.55
Absence	67	13.4				
The number of non-curative factor						
1	77	13.3	0.07			
≥2	33	3.85				
cT stage ^a						
T3, 4	97	9.43	0.27			
T1, 2	13	19.9				
Invasion to other organ						
Presence	35	3.30	0.01	-	-	-
Absence	75	14.1				
cN stage ^a						
N2, 3	81	6.88	0.03	1.80	1.04-3.26	0.03
N0, 1	29	22.5				
Histopathological type						
Undifferentiated	75	10.6	0.24			
Differentiated	35	11.3				
Preoperative chemotherapy						
Absence	81	12.0	0.43			
Presence	29	6.90				
Postoperative chemotherapy						
Absence	27	5.97	0.003	2.00	1.10-3.52	0.02
Presence	83	11.9				
Postoperative complication ^b						
Presence	22	6.13	0.11			
Absence	88	10.7				
Types of surgery						
Bypass	29	4.63	0.003	2.32	1.33-3.95	0.003
Gastrectomy	81	12.5				

^aAccording to the Japanese Classification of Gastric Carcinoma 3rd edition; ^bGrade 2 or higher according to the Clavien-Dindo classification; ^cValues are from Log-rank test; ^dp-Values are from Cox's proportional hazard model. M: Middle or lower third of stomach; U: upper third of stomach; cT: clinical T; cN: clinical N; OS: overall survival; HR: hazard ratio; CI: confidence interval.

($p=0.003$), and gastrojejunal bypass ($p=0.003$) were identified as prognostic factors associated with worse outcomes by univariate analysis. Multivariate analysis using the Cox proportional hazard model revealed that age [Hazard Ratio (HR)=1.93, 95% Confidence Interval (CI): 1.15-3.22, $p=0.01$], clinical N stage (HR=1.80, 95%CI=1.04-3.26, $p=0.03$), postoperative chemotherapy (HR=2.00, 95%CI=1.10-3.52, $p=0.02$), and types of surgery (HR=2.32, 95%CI=1.33-3.95, $p=0.003$) were independent prognostic factors.

Subgroup analysis of prognostic factors. A subgroup analysis of prognosis stratified by postoperative chemotherapy is shown in Figure 2. The 3-year OS of group G patients with postoperative chemotherapy was significantly better compared to group B patients ($p=0.03$; Figure 2A). However, no difference was seen in the patients without postoperative chemotherapy (Figure 2B). On the other hand, with regard to the prognosis stratified by age greater than 70 years, gastrectomy significantly contributed to a better

Postoperative chemotherapy

Figure 2. Subgroup analysis stratified by postoperative chemotherapy or age. (A, B) Overall survival using the Kaplan–Meier method is shown for patients with (A: n=83) or without (B: n=27) postoperative chemotherapy. (C, D) Overall survival using the Kaplan–Meier method is shown for patients with age less than 70 years (C: n=59) or more than 70 years (D: n=51).

prognosis compared to gastrojejunal bypass ($p=0.003$; Figure 2D). In patients younger than 70 years old, the difference was not significant ($p=0.10$; Figure 2C).

Table IV shows the frequency of postoperative chemotherapy stratified by age and the types of surgery. In patients older than 70 years old, the frequency of postoperative chemotherapy was significantly lower compared to patients under 70 ($p<0.001$), particularly in the group B compared to group G (43% versus 68%, $p=0.11$).

Discussion

The REGATTA trial has concluded that gastrectomy followed by chemotherapy does not show any survival benefits compared to chemotherapy alone in non-curable advanced gastric cancer (10). However, the REGATTA trial included only patients under 75 years of age with advanced gastric cancer and a single non-curable factor, and the patients received a single type of chemotherapy with TS1+ cisplatin.

Table IV. Frequency of postoperative chemotherapy stratified by age and type of surgery.

	Postoperative chemotherapy	Bypass n=29	Gastrectomy n=81	p-Value ^a	Total n=110	p-Value ^a
Age: <70	Presence	13 (87%)	39 (89%)	0.839	52 (88%)	<0.001
	Absence	2 (13%)	5 (11%)		7 (12%)	
Age: ≥70	Presence	6 (43%)	25 (68%)	0.107	31 (61%)	
	Absence	8 (57%)	12 (32%)		20 (39%)	

^ap-Values are from Chi-squared test.

The impact of a variety of chemotherapeutic regimens or resection in elderly patients remains unclear. In this study, 28 patients (97%) of Group B and 69 patients (86%) of group G were not eligible for the REGATTA criteria, and among these patients Group G showed significantly better 3-year OS compared to Group B (12.6% versus 4.85%, $p=0.01$).

In the present study, gastrectomy for patients with metastatic gastric cancer improved their survival compared to gastrojejunal bypass. The patients received various types of chemotherapies depending on their condition. A strong regimen is not suitable for every patient. Theoretically, gastrectomy may reduce the various symptoms or cytokines released by the primary tumor, thereby enhancing the systemic chemotherapy. It has also been shown that gastrectomy can reduce the number of tumor stem cells, possibly by increasing their sensitivity to palliative chemotherapy (15-18). These effects may possibly contribute to an improvement in the survival of patients following gastrectomy.

A subgroup analysis of prognosis stratified by postoperative chemotherapy has revealed that gastrectomy can imparted a survival benefit when combined with postoperative chemotherapy, whereas gastrectomy alone showed no survival benefit (Figure 2A and B). Moreover, in patients older than 70 years of age, the OS was better in group G compared to group B (Figure 2D). The low frequency of postoperative chemotherapy, particularly in elderly patients following gastrojejunal by-pass, may contribute to these results.

Univariate and multivariate analyses showed that postoperative chemotherapy, as well as gastrectomy were independent prognostic factors. We considered that chemotherapy is the standard of care for patients with metastatic gastric cancer. The main roles of palliative gastrectomy are to relieve cancer-related symptoms and to enhance the efficacy of chemotherapy, but not to cure the disease. Therefore, it is reasonable that gastrectomy itself has no survival benefit if not followed by postoperative chemotherapy and these results are consistent with other reports (19, 20).

In the present study, the frequency of postoperative complications of grade 2 or higher in group G was 22% (18/81), whereas the previously reported morbidity rate following palliative gastrectomy in patients with metastatic gastric cancer

ranged from 10.4 to 26% (19-21). There was no significant difference in the frequency of postoperative complications between groups G and B. Therefore, although the lengths of the hospital stays were longer in group G, we consider that our surgical outcomes are comparable to those of other reports (19-21), and that palliative gastrectomy for patients with metastatic gastric cancer is a safe and feasible treatment.

There were some limitations in this study. The sample size was too small, particularly for group B, to explore the role of the surgical strategy. In addition, presumably there were some selection and therapeutic biases due to the retrospective nature of the study. Moreover, due to the long-term patient registration and the lack of a standard treatment strategy for metastatic gastric cancer, there may have been inconsistencies regarding the postoperative chemotherapy regimen or indication for the types of surgery that should be followed. Most of therapeutic strategies were decided on a case-by-case basis.

In conclusion, although the present study was performed using limited case samples and has some inherent biases, it suggests that gastrectomy followed by postoperative chemotherapy in patients with metastatic gastric cancer may improve their survival compared to the gastrojejunal bypass. Further studies are needed to evaluate postoperative chemotherapy and its therapeutic effects in elderly patients.

Authors' Contributions

Matsubara D and Konishi H contributed equally to this study; Matsubara D, Konishi H and Otsuji E designed the research; Konishi H, Kosuga T, Kubota T and Okamoto K treated the patients and collected the data; Matsubara D and Konishi H analyzed the data; Matsubara D, Konishi H and Otsuji E wrote the manuscript.

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