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Prognostic significance of palliative gastrectomy in incurable advanced gastric cancer: a retrospective cohort study and meta-analysis

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Abstract. – OBJECTIVE: There is controversy regarding the role of palliative gastrectomy in patients with incurable advanced gastric cancer requiring surgical intervention. The present retrospective cohort study and meta-analysis aimed to determine whether palliative gastrectomy plus chemotherapy can prolong the survival of patients with incurable advanced gastric cancer requiring surgical intervention.

PATIENTS AND METHODS: The data from 153 patients diagnosed with incurable advanced gastric cancer requiring surgical intervention at our institute between January 2000 and December 2012 were retrospectively reviewed. We analyzed the value of palliative gastrectomy and identified the potential prognostic factors. We also conducted a meta-analysis of 10 studies to validate our results.

RESULTS: Multivariate analysis indicated that palliative gastrectomy was a favorable independent prognostic factor for prolonged overall survival in incurable advanced gastric cancer patients requiring surgical intervention (p=0.029). The median survival of patients who underwent palliative gastrectomy plus chemotherapy was significantly longer than that of those who underwent non-resection surgery plus chemotherapy (12 months *vs.* 9 months, p=0.020). The patients in the non-resection surgery plus chemotherapy group exhibited significantly shorter overall survival than those in the D1+ lymphadenectomy group, D2 lymphadenectomy group, or distal gastrectomy group (p=0.021, p=0.007, and p=0.006, respectively). Our meta-analysis revealed that gastrectomy plus chemotherapy improved long-term survival in incurable advanced gastric cancer patients (hazard ratio (HR): 0.48; 95% confidence interval (CI): 0.35-0.67; p<0.001).

CONCLUSIONS: Palliative gastrectomy plus chemotherapy may improve overall patient survival compared with non-resection operations plus chemotherapy in incurable advanced gastric cancer patients requiring surgical intervention.

Key Words:
Gastric cancer, Incurable, Palliative gastrectomy, Metastasis.

Abbreviations

IAGC = Incurable advanced gastric cancer; PG = palliative gastrectomy; NR = non-resection; OS = overall survival.

Introduction

Gastric cancer was the third leading cause of cancer-related mortality worldwide in 2018[1]. According to the Surveillance Epidemiology and End Results (SEER) Database, 34% of the patients had gastric tumors that had metastasized to distant organs at the time of the initial examination[2]. Incurable advanced gastric cancer (IAGC) refers to unresectable locally advanced or metastatic gastric cancer[3]. Chemotherapy is considered the standard treatment for patients with IAGC[4-6]. However, the long-term outcomes for IAGC patients treated with chemotherapy alone are dismal; the 5-year survival rates rarely exceed 15%. Palliative surgery is an option for IAGC patients who present with serious symptoms, such as obstruction, perforation and bleeding, and cannot be treated with conventional chemotherapy. Palliative surgery includes palliative gastrectomy (PG) with primary lesion excision and bypass surgery without primary lesion excision. PG for IAGC patients with serious symptoms can improve the quality of life (QOL) and nutritional status and provide conditions for further treatment. Symptoms may also be resolved when

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bypass surgery is performed for IAGC patients with serious symptoms. The selection of PG or short-circuit surgery depends on the resectability of and/or surgical risks associated with the primary tumor[4]. Currently, it is not clear whether there is a difference in the postoperative survival between IAGC patients with serious symptoms who undergo PG and those who undergo bypass surgery. The optimal treatment strategy for IAGC is debatable worldwide to date, partly because the effect of PG on survival is not explicit[7-13]. Historically, the postoperative mortality rates after PG are high, and the operation is technically difficult when the tumor grows and invades the adjacent organs of the patients with IAGC[14]. Recent advancements in the patient selection strategies, operating techniques, methods of anesthesia methods, nutritional support and development of new antibiotics have reduced the postoperative mortality to 0-5%[10,15,16]. Owing to this decrease, the effects of PG on the overall survival (OS) of patients with IAGC are being reevaluated. The fourth edition of the treatment guidelines of the Japanese Gastric Cancer Association (JGCA) states that PG may serve as an alternative therapeutic strategy for IAGC patients without major symptoms[4]. Several retrospective cohort studies and meta-analyses[7,11,17-26] have reported that gastrectomy may provide some survival benefits to patients with IAGC. In contrast, some studies have reported that gastrectomy does not confer a survival advantage in IAGC patients[10,27-29]. Most of the patients included in the aforementioned studies were asymptomatic or it was not sure whether they had symptoms or not. To date, it is not clear whether PG can prolong the survival of IAGC patients requiring surgical intervention for symptoms, such as obstruction, perforation, and bleeding. Thus, the present study aimed to 1) identify the prognostic factors of patients with IAGC; 2) assess the therapeutic effects of PG plus chemotherapy on the survival of IAGC patients; and 3) determine the prognostic factors for selecting appropriate candidates for PG plus chemotherapy.

Patients and Methods

Patients

The data of 153 patients admitted to the Department of Surgical Oncology of the First Affiliated Hospital of China Medical University with pathologically confirmed IAGC between January 2000 and December 2012 were retrospectively reviewed. All 153 patients presented with obstruction, perforation, or bleeding; thus, these patients were unsuitable for routine chemotherapy and required surgical treatment for the resolution of their symptoms. The patients were divided into a palliative gastrectomy plus chemotherapy group (PG+C group, n=104) and a non-resection surgery plus chemotherapy group (NR+C group, n=49).

The incurable factors in these patients with advanced gastric cancer were unresectable locally advanced cancer (tumor residue or lymph node residue), peritoneal metastasis, liver metastasis, ovary metastasis, and peritoneal and liver metastasis. Metastasis was defined, based on the preoperative computed tomography (CT), pathologic biopsy, and intraoperative findings. PG included distal gastrectomy, proximal gastrectomy, and total gastrectomy with D1 (32.7%), D1+ (19.2%), D2 (45.2%), or D3 (2.9%) lymphadenectomy. The non-resection surgeries included bypass surgery (gastrojejunostomy, jejunostomy, gastrostomy, and other such procedures), perforation repair, local suture hemostasis, or gastric vessel ligation. As there is no standard surgical procedure for IAGC patients requiring surgical intervention, the surgical team decided on a case-by-case basis whether PG or non-resection surgery should be performed. None of the patients received preoperative chemotherapy or radiotherapy and the patients with distant visceral organ metastasis did not undergo metastasectomy. Patients diagnosed with primary cancer other than gastric cancer were excluded. Patients who died within one month after surgery were excluded. The TNM stage was defined according to the AJCC eighth edition guidelines. All patients received at least six cycles of postoperative chemotherapy with 5-fluorouracil-based or platinum-based regimen.

The complete study population was followed-up *via* outpatient clinic consultation and/or phone communication till mortality was reported or till the date of the last scheduled follow-up (December 31, 2017). The study protocol was approved by the Institutional Ethics Committee of China Medical University.

Statistical Analysis

The chi-square test was used to compare the categorical variables. The OS was analyzed using Kaplan-Meier analysis and compared using the log-rank test. Multivariate analysis for identify-

ing the prognostic factors was conducted using a Cox regression model. The HRs (hazard ratios) and 95% confidence intervals (95% CIs) were estimated using a Cox regression model. A two-tailed value of $p<0.05$ was considered statistically significant. All statistical analyses were performed using the Statistical Package for the Social Sciences version 24.0 for Windows (SPSS Inc., Armonk, NY, USA).

Meta-Analysis

We searched all articles published in English on the PubMed, EMBASE, and Cochrane Library databases before November 2019. The search terms included "neoplasm* OR cancer* OR carcinoma" AND "stomach OR gastric OR (Stomach Neoplasms)" AND "stage IV OR late-stage OR metastat* OR peritoneal OR liver OR hepatic"AND "gastrectomy OR reduct*", and the search strategy was changed according to the different requirements for each database to ensure that all relevant literature was completely reviewed. Some patients with IAGC in the included studies were asymptomatic or were not sure whether they had symptoms or not. Aside from this, the inclusion and exclusion criteria were the same as those for the retrospective cohort study. The extracted survival data were used to calculate the HRs and 95% CIs, to identify the potential associations with the OS in the two groups. Heterogeneity between studies was examined using a combination of the Cochran's Q (chi-square) test and the I^2 statistic. If the heterogeneity was statistically significant, a random-effects model was used. Statistical analysis was performed using STATA software version 12.0 (Stata Corporation, College Station, TX, USA).

Results

Patients Characteristics

The characteristics of 153 patients with IAGC requiring surgical intervention are detailed in Table I. The PG+C group had more younger patients (<50 years old) and fewer older patients (≥ 70 years old) than the NR+C group (p=0.027). In the PG+C group, gastrectomy for D1 lymphadenectomy was performed for 32.7% of the patients; for D1+ lymphadenectomy, 19.2% of the patients; for D2 lymphadenectomy, 45.2% of the patients; and for D3 lymphadenectomy, 2.9% of the patients. No differences were found between the PG+C and NR+C groups with respect to postoperative mortality within 3 months, which indicated that PG plus chemotherapy did not increase the postoperative mortality within 3 months.

Identifying the Prognosis Factors for IAGC Patients

Univariate analysis indicated that PG and Borrmann type were the prognostic factors for the OS (p=0.020 and p=0.038, respectively; Table II). Multivariate analysis showed that PG was an independent prognostic factor (p=0.029; Table II).

Effect of PG on the IAGC Patients

We analyzed the effect of PG on the IAGC patients requiring surgical intervention. The median survival was significantly longer for the patients in the PG+C group than for those in the NR+C group (12 months *vs.* 9 months; HR for PG: 0.67, 95% CI 0.47-0.95, p=0.020; Figure 1A).

We then divided the PG+C group into the D1, D1+, and D2 lymphadenectomy groups, according to the range of lymph node dissection, and compared the OS of these groups with that of the NR+C group. The OS was significantly shorter for the patients in the NR+C group than for those in the D1+ and D2 groups (p=0.021 and p=0.007, respectively; Figure 1B). The OS of the patients in the D1 group was similar to that of those in the NR+C group (p=0.929; Figure 1B).

The PG+C group was further divided into the distal gastrectomy group and the total gastrectomy group, according to the surgical procedure, and the OS of these subgroups was compared with that of the NR+C group. The OS of patients in the NR+C group was significantly shorter than that of those in the distal gastrectomy group (p=0.006; Figure 1C), while it was similar to that of those in the total gastrectomy group (p=0.754; Figure 1C).

Subgroup Analysis

A subgroup analysis was conducted to evaluate the association of PG with other variables and to identify the potential subsets of patients who will benefit from PG. Among the investigated variables, patient age of 50-59 years (HR: 0.46 [95% CI: 0.23-0.95], p=0.036), male sex (HR: 0.62 [95% CI: 0.41-0.93], p=0.020), Borrmann type III (HR: 0.66 [95% CI: 0.45-0.97], p=0.032), Borrmann type IV (HR: 0.28 [95% CI: 0.11-0.70], p=0.007), and peritoneal metastasis with D2 lymphadenectomy (HR: 0.58 [95% CI: 0.38-0.88], p=0.010) were identified as the factors that improve OS after PG (Figure 2).

Table I. Clinicopathological characteristics of patients with incurable advanced gastric cancer.

Characteristics	PG + C group (n = 104)	NR + C group (n = 49)	*p*-value
Age group, n (%)			0.027[d]
< 50 years	40 (38.5)	9 (18.4)	
50-59 years	24 (23.0)	14 (28.6)	
60-69 years	32 (30.8)	16 (32.7)	
> 70 years	8 (7.7)	10 (20.3)	
Gender, n (%)			0.658[d]
Male	75 (72.1)	37 (75.5)	
Female	29 (27.9)	12 (24.5)	
Charlson comorbidity index score, n (%)			0.180[d]
0	17 (16.4)	3 (6.1)	
1	12 (11.5)	4 (8.2)	
2	26 (25.0)	15 (30.6)	
3	34 (32.7)	14 (28.6)	
≥ 4	15 (14.4)	13 (26.5)	
T stage[ab], n (%)			0.074[d]
T3	36 (34.6)	10 (20.4)	
T4	68 (65.4)	30 (79.6)	
Location of primary tumor, n (%)			0.642[d]
Upper third	3 (2.9)	1 (2.0)	
Middle third	13 (12.5)	10 (20.4)	
Lower third	67 (64.4)	29 (59.2)	
Entire stomach[c]	21 (20.2)	9 (18.4)	
Borrmann type[b], n (%)			0.125[d]
III	83 (79.8)	44 (89.8)	
IV	21 (20.2)	4 (10.2)	
Incurable factor, n (%)			0.101[d]
Unresectable locally advanced	19 (18.3)	18 (36.7)	
Peritoneal metastasis	64 (61.5)	25 (51.0)	
P0CY1	10	0	
P1, P2, P3	54	25	
Liver metastasis	16 (15.4)	4 (8.2)	
H1	15	4	
H3	1	0	
Ovary metastasis	2 (1.9)	NA	
Peritoneal +Liver metastasis	3 (2.9)	2 (4.1)	
Surgical procedure, n			
Proximal gastrectomy	1	NA	
Distal gastrectomy	62	NA	
Total gastrectomy	41	NA	
Non-resection surgery	NA	49	
Lymphadenectomy, n			
D1	34	NA	
D1+	20	NA	
D2	47	NA	
D3	3	NA	
Postoperative mortality within 3 months, n (%)	5	4	0.410[d]

Data are shown as number of patients n (%), as indicated. NA: not applicable. [a]Based on AJCC Cancer Staging Manual, 8th edition. [b]PG+C group denotes pathological findings and NR+C group denotes clinical findings. [c]Primary tumor in the upper, middle and lower stomach. [d]*p*-value is the result of comparison of PG+C group and NR+C group.

Identifying the Prognosis Factors for the IAGC Patients Undergoing PG

Univariate and multivariate survival analyses were performed for patients in the PG+C group to evaluate the effect of different clinicopathological factors associated with PG (Table III). Univariate analysis showed that distal gastrectomy and D1+ and D2 lymphadenectomies were the favorable prognostic factors for prolonged OS (p=0.011 and p=0.015, respectively). Multivariate analysis indicated that incurable factors were the independent prognostic factors for OS (p=0.046).

Table II. Univariate and multivariate analysis of prognostic factors for patients with incurable advanced gastric cancer.

Variable	Univariate analysis				Multivariate analysis[d]	
	Median survival[b] (95% CI)	1-year survival (%)	2-year survival (%)	*p*-value	Hazard ratio (95% CI)	*p*-value
Age group				0.13		
< 50 years[c]	11 (8.95-13.05)	44.9	16.3			
50-59 years	13 (9.38-16.62)	55.3	28.9			
60-69 years	9 (7.15-10.85)	37.5	16.7			
70+ years	9 (6.65-11.35)	33.3	5.6			
Gender				0.73		0.346
Male[c]	10 (8.76-11.24)	42	20.5		1 (-)	
Female	12 (9.31-14.69)	48.8	12.2		1.23 (0.80-1.89)	
Charlson comorbidity index score				0.965		0.763
0[c]	11 (8.08-13.92)	45	15		1 (-)	
1	10(6.08-13.92)	50	18.8		1.29 (0.62-2.67)	
2	10 (7.91-12.09)	43.9	19.5		0.97 (0.53-1.77)	
3	9 (6.74-11.26)	41.7	18.8		1.27 (0.71-2.28)	
4	9 (6.43-11.57)	42.9	17.9		1.21 (0.65-2.27)	
Palliative gastrectomy				0.02		0.029
No[c]	9 (7.66-10.34)	32.7	12.2		1 (-)	
Yes	12 (9.86-14.14)	49	21.2		0.65 (0.44-0.96)	
Location of primary tumor				0.106		0.232
Upper third[c]	10 (9.15-10.85)	25	0		1 (-)	
Middle third	9 (7.45-10.55)	30.4	4.3		0.93 (0.28-3.06)	
Lower third	11 (8.44-13.56)	47.9	25		0.57 (0.19-1.72)	
Entire stomach[e]	10 (6.78-13.22)	43.3	10		0.66 (0.20-2.23)	
Borrmann type				0.038		0.078
III[c]	11 (8.80-13.21)	45.7	21.3		1 (-)	
IV	10 (7.51-12.49)	34.6	3.8		1.69 (0.94-3.01)	
pT stage[a]				0.148		0.317
T3[c]	14 (10.22-17.78)	54.3	15.2		1 (-)	
T4	10 (8.83-11.17)	39.3	19.6		1.22 (0.83-1.79)	
Incurable factor				0.598		0.324
Unresectable locally advanced[c]	9 (7.52-10.49)	40.5	27		1 (-)	
Peritoneal metastasis	12 (9.87-14.13)	48.3	15.7		0.91 (0.57-1.44)	
Liver metastasis	9 (7.93-10.07)	30	15		1.47 (0.82-2.66)	
Ovary metastasis	24 (-)	100	50		0.37 (0.07-2.05)	
Peritoneal+Liver metastasis	11 (4.56-17.44)	20	0		1.31 (0.48-3.60)	

[a]Based on AJCC Cancer Staging Manual, 8th edition. [b]Months. [c]Reference group. [d]Considering the interaction between age and Charlson comorbidity index score factors, age was not included in the multivariate analysis. [e]Primary tumor in the upper, middle and lower stomach.

Characteristics of the Patients with Long-Term Survival (>2 years) After PG

The survival time of 25 patients in the PG+C group was >2 years. The characteristics of clinical pathologic factors distribution are shown in Table IV. The patients with long-term survival were distributed more in the following subgroups: aged 50-59 years, male, primary tumor located in the lower third, Borrmann type III, histologic grade is well and moderately differentiated, unresectable locally advanced, ovary metastasis, lymphatic invasion is negative, ratio between metastatic lymph nodes and examined lymph nodes ≤0.5, distal gastrectomy, and D2 lymphadenectomy.

Meta-Analysis of the Prognostic Significance of PG in the IAGC Patients

From among the studies identified in our literature review, we included 10 studies, all of which reported patient OS data[7,10,17-22,26,30] and these data were added to our meta-analysis. All 17,876 patients from the 10 studies were eligible for the final analysis. The HR for the OS was 0.49 (95% CI: 0.35-0.67; $p<0.001$; Figure 3), and significant heterogeneity was observed among the studies ($p<0.001$, $I^2=92.0\%$; Figure 3). The sensitivity analysis results were computed by omitting each study in turn. The heterogeneity decreased from 92.0% to 75.9% when the study by Sougioultzis

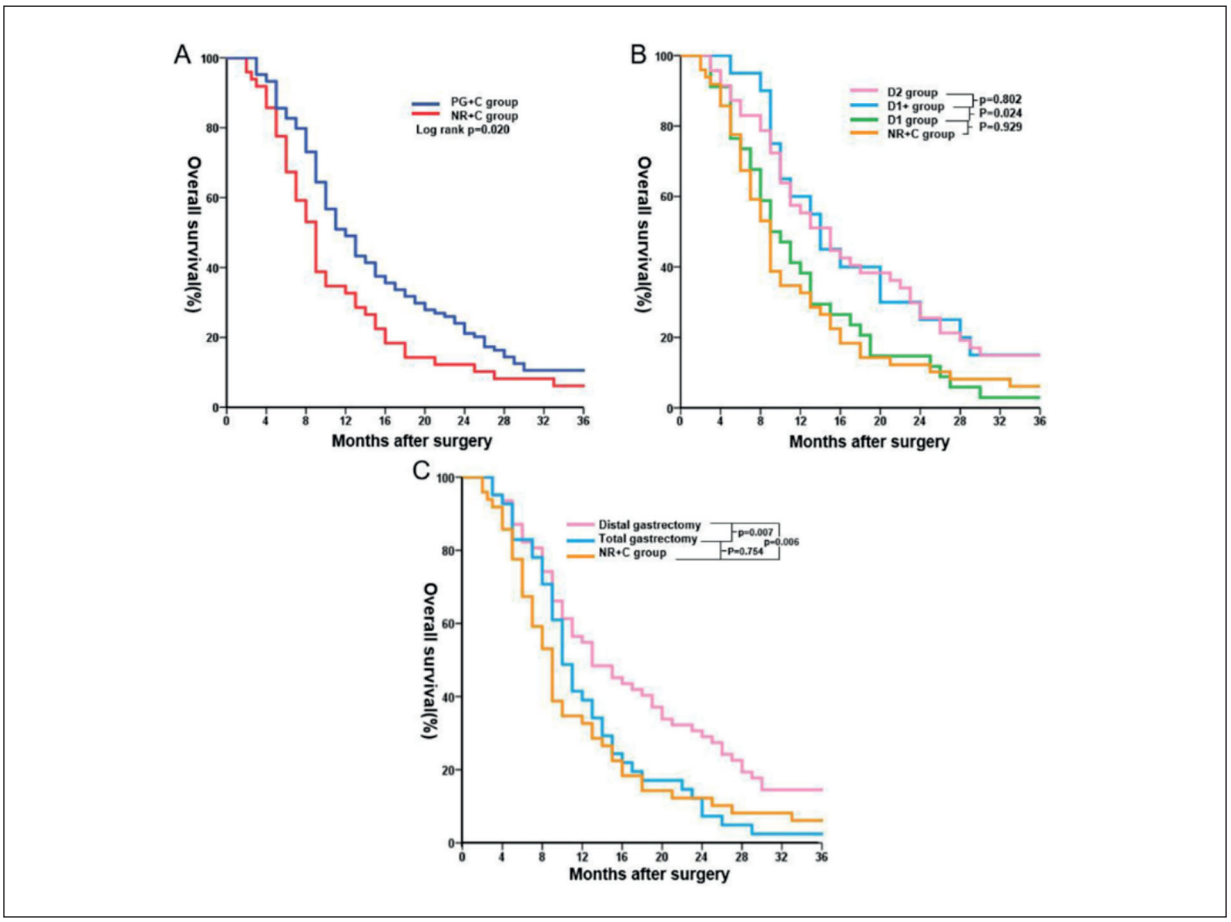

Figure 1. Overall survival of patients with incurable advanced gastric cancer (**A**) treated with or without palliative gastrectomy; (**B**) treated with D1, D1+, and D2 lymphadenectomy, and without palliative gastrectomy; (**C**) treated with distal gastrectomy, total gastrectomy, and without palliative gastrectomy.

et al[21] was removed. We, therefore, removed this study from the meta-analysis, because most patients in this study received a single-agent chemotherapy regimen. The patients in the other nine studies mostly received combination chemotherapy regimens. After the study by Sougioultzis et al[21] was removed, the combined effect was not change in statistically significantly (HR: 0.58; 95% CI: 0.48-0.71; p<0.001; Figure 4). A subgroup analysis according to the study type was conducted to identify the causes of heterogeneity in 10 included studies (Figure 4). All studies were retrospective cohort studies, except for the study by Fujitani et al[10], which was a randomized controlled trial (RCT). In the retrospective cohort study subgroup, the between-study heterogeneity was not significant (p=0.003, I^2=65.7%). Therefore, we considered that the significance between study heterogeneity may be attributable to the different study types and chemotherapy regimens. This meta-analysis showed that gastrectomy plus chemotherapy may improve the long-term survival of patients with IAGC (HR: 0.49; 95% CI: 0.35-0.67; p<0.001; Figure 3).

Discussion

Currently, an increasing amount of attention is being paid to primary tumor resection in patients with metastatic disease. However, the effect of PG combined with chemotherapy is not clear to date. The findings of this study indicated that PG plus chemotherapy was associated with significantly improved OS compared with non-resection surgery plus chemotherapy in patients with IAGC requiring surgical intervention.

Several studies[7,11,17-22,25,26] have reported that PG followed by chemotherapy confers a survival benefit in patients with IAGC. Yang et

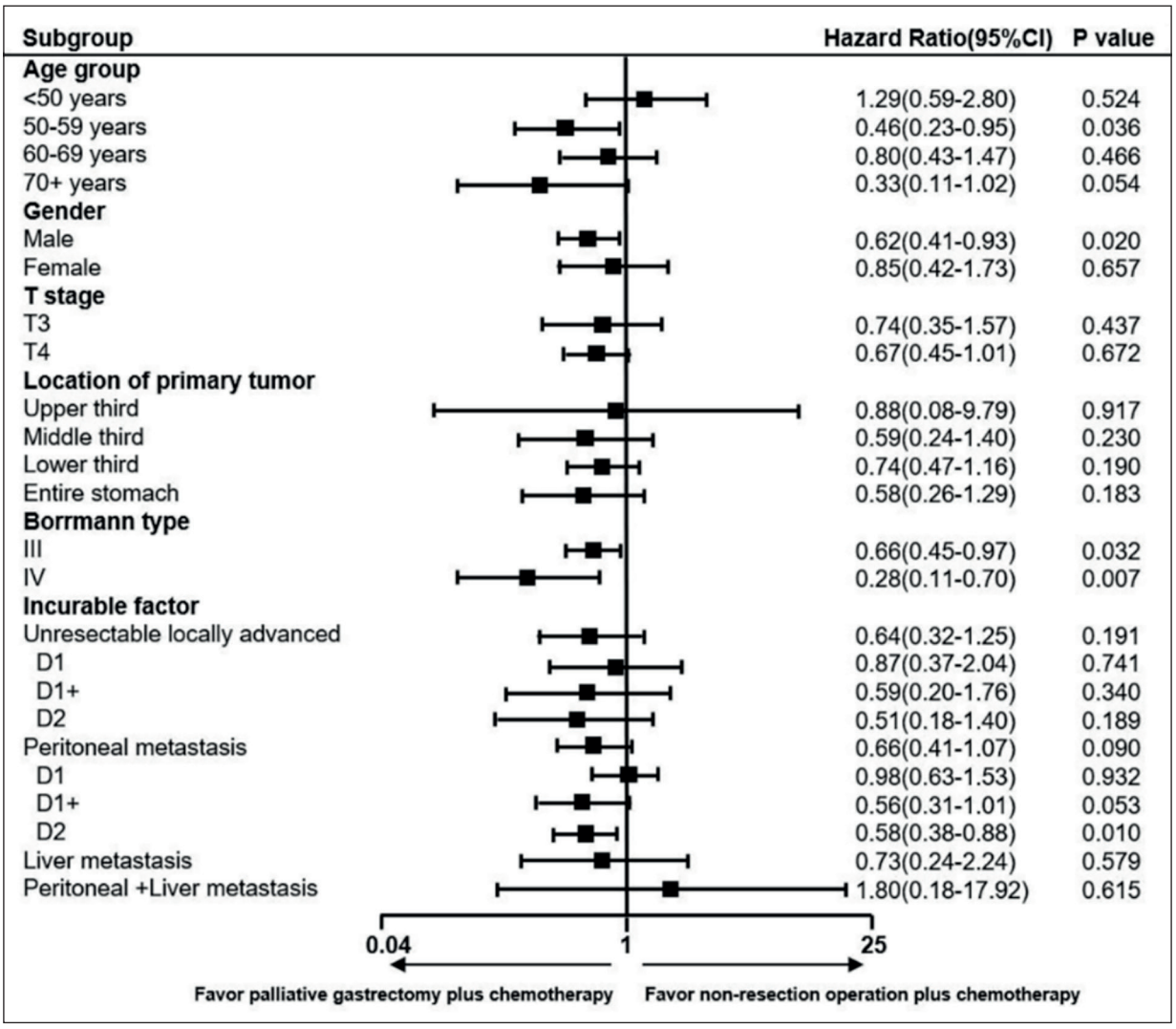

Figure 2. Subgroup analysis of palliative gastrectomy plus chemotherapy (PG+C group) and non-resection operation plus chemotherapy (NR+C group) among incurable advanced gastric cancer patients.

al[26] conducted a study based on data from the SEER database and suggested that gastrectomy plus metastasectomy or gastrectomy alone could improve survival in gastric cancer patients with synchronous metastasis. Warschkow et al[7] reported that gastrectomy could improve survival from chemotherapy alone, based on the analysis of the data of a large sample of 7,026 metastatic gastric cancer patients, diagnosed during 2006-2012, archived in the National Cancer Database. A meta-analysis of 13 published articles, involving 2,368 IAGC patients conducted by Wu et al[23], indicated that PG plus chemotherapy can improve the OS (HR: 0.43; 95% CI: 0.29-0.65, $p<0.0001$). Lasithiotakis et al[24] conducted a meta-analysis of 19 studies including 2,911 patients with stage IV gastric cancer, and found that the 1-year OS was significantly improved for patients who underwent gastrectomy compared to that for those who underwent non-resectional treatment (odds ratio: 2.6, 95% CI: 1.7-4.3, $p<0.0001$). This analysis also showed improvement in the quality of life (QOL) and symptoms after PG. The results of the GYMSSA trial concluded that complete cytoreductive surgery combined with hyperthermic intraoperative peritoneal chemotherapy (HIPEC) and systemic chemotherapy may improve the OS to a greater extent than systemic chemotherapy alone[31].

In contrast, an RCT comparing gastrectomy and chemotherapy with chemotherapy alone (REGATTA trial) reported that gastrectomy conferred

Table III. Univariate and multivariate analysis of prognostic factors for patients with incurable advanced gastric cancer undergoing palliative gastrectomy.

Variable	Univariate analysis		Multivariate analysis[c]	
	Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value
Age group		0.158		
< 50 years[b]	1 (-)			
50-59 years	0.57 (0.33-0.98)			
60-69 years	0.98 (0.60-1.58)			
70+ years	0.91 (0.42-1.96)			
Gender		0.428		0.688
Maleb	1 (-)		1 (-)	
Female	1.20 (0.77-1.87)		1.18 (0.53-2.62)	
Charlson comorbidity index score		0.536		0.498
0[b]	1 (-)		1 (-)	
1	0.93 (0.44-1.96)		2.03 (0.70-5.93)	
2	0.60 (0.31-1.15)		0.76 (0.28-2.08)	
3	0.70 (0.39-1.28)		1.00 (0.40-2.47)	
4	0.66 (0.32-1.35)		0.77 (0.26-2.23)	
Location of primary tumor		0.442		0.211
Upper third[b]	1 (-)		1 (-)	
Middle third	1.05 (0.30-3.74)		1.24 (0.17-9.08)	
Lower third	0.72 (0.22-2.31)		0.72 (0.11-4.90)	
Entire stomach[d]	1.02 (0.30-3.41)		0.39 (0.05-2.86)	
Tumor size		0.378		0.682
< 5 cm[b]	1 (-)		1 (-)	
≥ 5 cm	1.22 (0.78-1.89)		0.87 (0.44-1.71)	
Histologic grade		0.163		0.148
Well differentiated[b]	1 (-)		1 (-)	
Moderately differentiated	1.66 (0.39-7.15)		0.91 (0.13-6.39)	
Poorly differentiated	2.30 (0.56-9.43)		1.89 (0.31-11.60)	
Undifferentiated	0.86 (0.12-6.13)		0.47 (0.02-12.42)	
Borrmann type		0.065		0.272
III[b]	1 (-)		1 (-)	
IV	1.62 (0.99-2.66)		1.72 (0.65-4.54)	
pT stage[a]		0.39		0.672
T3[b]	1 (-)		1 (-)	
T4	1.21 (0.78-1.86)		1.14 (0.62-2.09)	
pN stage[a]		0.259		0.267
N0[b]	1 (-)		1 (-)	
N1	2.35 (0.90-6.16)		3.26 (0.81-13.12)	
N2	1.40 (0.62-3.20)		1.01 (0.31-3.26)	
N3	1.78 (0.84-3.80)		1.02 (0.33-3.17)	
Incurable factor		0.562		0.046
Unresectable locally advanced[b]	1 (-)		1 (-)	
Peritoneal metastasis	1.19 (0.69-2.04)		0.82 (0.33-2.04)	
Liver metastasis	1.50 (0.75-3.01)		2.60 (0.96-7.07)	
Ovary metastasis	0.68 (0.16-2.93)		0.09 (0.01-1.87)	
Peritoneal+Liver metastasis	2.24 (0.64-7.80)		0.97 (0.13-7.26)	
Resection margins		0.671		0.989
Negative[b]	1 (-)		1 (-)	
Positive	1.30 (0.41-4.13)		0.99 (0.18-5.47)	
Vascular invasion		0.295		0.573
Negative[b]	1 (-)		1 (-)	
Positive	1.51 (0.73-3.14)		0.73 (0.24-2.21)	
Lymphatic invasion		0.211		0.378
Negative[b]	1 (-)		1 (-)	
Positive	1.32 (0.86-2.02)		0.77 (0.42-1.39)	

Continued

Table III ***(Continued).*** Univariate and multivariate analysis of prognostic factors for patients with incurable advanced gastric cancer undergoing palliative gastrectomy.

Variable	Univariate analysis		Multivariate analysis[c]	
	Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value
Ratio between metastatic lymph nodes and examined lymph node		0.129		0.477
≤ 0.5[b]	1 (-)		1 (-)	
> 0.5	1.44 (0.91-2.27)		1.34 (0.60-3.04)	
No. of examined lymph node		0.639		0.677
< 15[b]	1 (-)		1 (-)	
≥ 15	0.88 (0.53-1.47)		0.84 (0.36-1.94)	
Surgical procedure		0.011		0.179
Distal gastrectomy[b]	1 (-)		1 (-)	
Total gastrectomy	1.74 (1.14-2.64)		2.04 (0.72-5.74)	
Lymphadenectomy		0.015		0.344
D1	1 (-)		1 (-)	
D1+	0.53 (0.29-0.94)		1.28 (0.53-3.08)	
D2	0.56 (0.36-0.89)		0.77 (0.33-1.80)	
D3	2.03 (0.61-6.75)		2.32 (0.46-11.7)	

[a]Based on AJCC Cancer Staging Manual, 8th edition. [b]Reference group. [c]Considering the interaction between age and Charlson comorbidity index score factors, age was not included in the multivariate analysis. [d]Primary tumor in the upper, middle and lower stomach.

no benefit[10]. All the patients in the REGATTA trial were asymptomatic, and the test group in the REGATTA trial underwent reduction surgery. Therefore, the efficacy of gastrectomy for IAGC patients with symptoms requiring surgical intervention is not clear. There are a few differences between the present study and the REGATTA trial. First, gastrectomy was restricted to D1

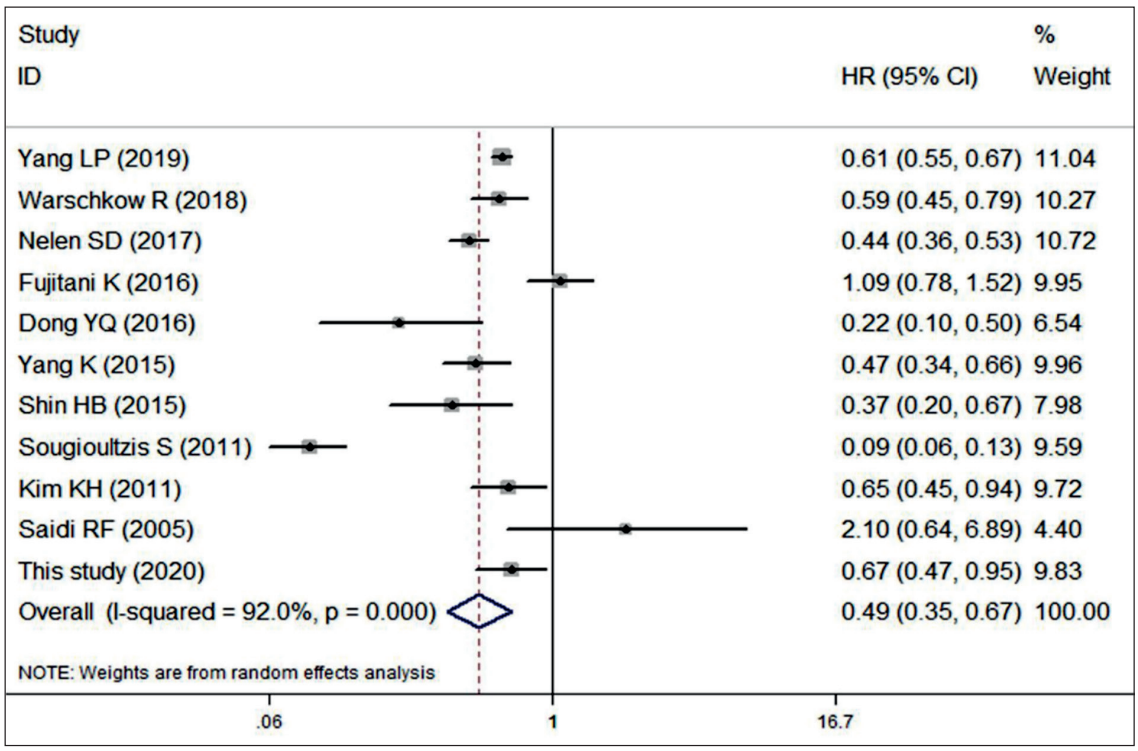

Figure 3. Meta-analysis of prognostic significance of palliative gastrectomy in incurable advanced gastric cancer patients.

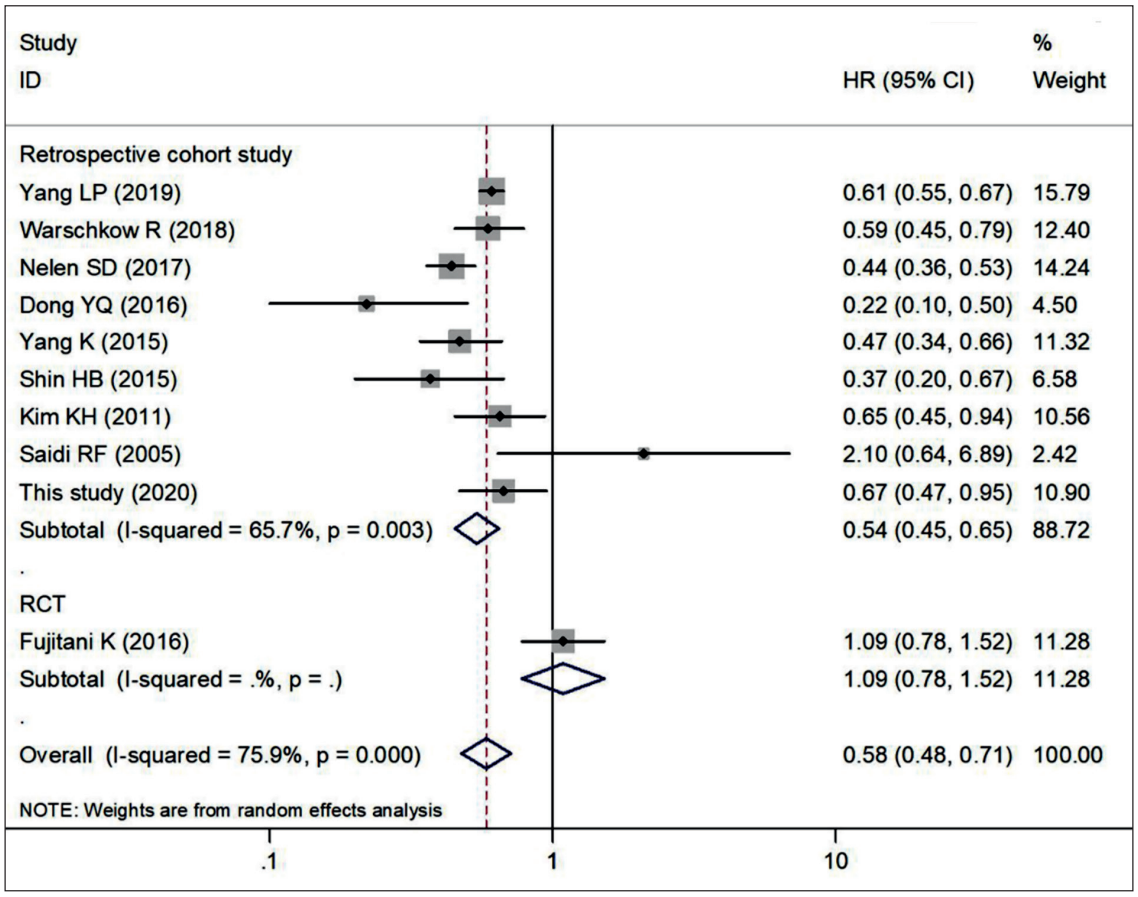

Figure 4. Subgroup analysis by study type.

lymphadenectomy in the REGATTA trial. In the present study, D1+, D2, and D3 lymphadenectomies were performed in 67.3% of the patients. Second, the REGATTA trial included patients with liver, peritoneal, or para-aortic lymph node metastases; thus, the effect of gastrectomy on the survival of patients with unresectable locally advanced gastric cancer remains unclear[18]. In the current study, we included patients with unresectable locally advanced gastric cancer. Third, we carefully grouped patients according to the clinicopathological characteristics and compared the effect of PG on the patient prognosis to identify the population that would benefit from PG. However, a large-scale RCT involving patients from the Eastern and Western countries is warranted to validate our findings.

In our study, the decision to perform PG or non-resection surgery was made by the surgical team on a case-by-case basis. Doctors sometimes prefer PG, even if the tumor had invaded the adjacent organs of the patients in the PG+C and NR+C groups differed statistically significantly with respect to age. The patients in the PG+C group were significantly younger than those in the NR+C group. Owing to the better physical condition and surgical tolerance of the younger patients than of the older patients, surgeons consider younger patients more suitable for PG. No statistically significant difference was observed in the distribution of the other clinicopathological characteristics between the two groups. However, surgeons still tended to select patients with T3 stage and P0CY1 disease for PG; this may be because these patients presented with mild disease. Surgeons also tend to choose patients with Borrmann type IV for undergoing PG, which may be because of tumor invasion and the inability of doctors to find a suitable gastric wall area for anastomosis.

The scope of lymphadenectomy in the PG+C group was also determined at the discretion of the surgical team on a case-by-case basis in the present analysis. The median survival of pa-

Table IV. The characteristics of patients with long-term survival (> 2 years) after palliative gastrectomy.

Variable	Patients with long-term survival, n (%)	PG+C group, n (%)
Age group		
< 50 years	8 (32.0)	40 (38.5)
50-59 years	9 (36.0)	24 (23.0)
60-69 years	7 (28.0)	32 (30.8)
70 + years	1 (4.0)	8 (7.7)
Gender		
Male	20 (80.0)	75 (72.1)
Female	5 (20.0)	29 (27.9)
Location of primary tumor		
Upper third	1 (4.0)	3 (2.9)
Middle third	1 (4.0)	13 (12.5)
Lower third	20 (80.0)	67 (64.4)
Entire stomach	3 (12.0)	21 (20.2)
Tumor size		
< 5 cm	9 (36.0)	35 (34.7)
≥ 5 cm	16 (64.0)	66 (65.3)
Borrmann type		
III	24 (96.0)	83 (79.8)
IV	1 (4.0)	21 (20.2)
pT stage		
T3	8 (32.0)	36 (34.6)
T4	17 (68.0)	68 (65.4)
pN stage		
N0	4 (16.0)	11 (11.6)
N1	3 (12.0)	9 (9.5)
N2	6 (24.0)	24 (25.3)
N3	12 (48.0)	51 (53.7)
Resection margins		
Negative	24 (96.0)	101(97.1)
Positive	1 (4.0)	3 (2.9)
Histologic grade		
Well differentiated	2 (8.3)	2 (1.9)
Moderately differentiated	7 (29.2)	20 (19.4)
Poorly differentiated	14 (58.3)	78 (75.8)
Undifferentiated	1 (4.2)	3 (2.9)
Incurable factor		
Unresectable locally advanced	7 (28.0)	19 (18.8)
Peritoneal metastasis	13 (52.0)	64 (63.4)
Liver metastasis	3 (12.0)	16 (15.8)
Ovary metastasis	2 (8.0)	2 (2.0)
Vascular invasion		
Negative	24 (96.0)	96 (92.3)
Positive	1 (4.0)	8 (7.7)
Lymphatic invasion		
Negative	18 (75.0)	65 (63.7)
Positive	6 (25.0)	37 (36.3)
Ratio between metastatic lymph nodes and examined lymph node		
≤ 0.5	21 (84.0)	66 (69.5)
> 0.5	4 (16.0)	29 (30.5)
No. of examined lymph node		
< 15	4 (16.0)	20 (21.1)
≥ 15	21 (84.0)	75 (78.9)
Surgical procedure		
Proximal gastrectomy	1 (4.0)	1 (1.0)
Distal gastrectomy	19 (76.0)	62 (59.6)
Total gastrectomy	5 (20.0)	41 (39.4)
Lymphadenectomy		
D1	5 (20.0)	34 (33.7)
D1+	6 (24.0)	20 (19.8)
D2	14 (56.0)	47 (46.5)

tients undergoing D1+ or D2 lymphadenectomy was significantly longer than that of patients undergoing D1 lymphadenectomy or non-resection surgery plus chemotherapy. The extent of lymphadenectomy may play a role in reducing the load of lymph node metastasis.

The present study showed that palliative distal gastrectomy conferred a survival benefit compared with non-resection surgery in IAGC patients requiring surgical intervention, while no difference in survival was observed between palliative total gastrectomy and non-resection surgery. Similarly, the REGATTA trial showed that in patients with tumors located in the upper third of stomach who underwent total gastrectomy, the median chemotherapy cycle after total gastrectomy was half that of chemotherapy alone. This suggests that reduced chemotherapy compliance after total gastrectomy resulted in shorter survival. In contrast, patients who received distal gastrectomy showed good compliance with chemotherapy[10]. In the current study, no significant difference was observed with respect to the chemotherapy cycles between the palliative distal gastrectomy group and the palliative total gastrectomy group, suggesting that palliative distal gastrectomy may play a role in reducing the tumor load.

There are some limitations of the present study. First, our sample size was small, and all patients were from a single institution; moreover, this was a retrospective study. Therefore, selection bias may be present. Second, the decision to perform either PG or non-resection surgery was made by the surgical team based on a case-by-case analysis. Third, we did not have information regarding the performance status, QOL measures, and detailed chemotherapy regimen. In addition, the patients included in the study did not undergo evaluation of HER-2 expression, although it affects the prognosis[32]. Fourth, the heterogeneity between the included studies was evident from the results of the meta-analysis. The studies included in this meta-analysis differed with respect to the ethnicity of the patients, study type (retrospective cohort studies *vs.* RCTs), and treatment administered (single-agent chemotherapy regimen *vs.* combination chemotherapy regimens, chemotherapy *vs* chemotherapy with non-resection surgery), all these factors significantly contributed to the heterogeneity among the included studies.

Recently, two RCTs have been initiated in France and China to evaluate the value of gastrectomy followed by chemotherapy in advanced gastric cancer patients, and the results are keenly awaited[33,34]. Similarly, surgical resection following chemotherapy may draw attention in future studies to prolong the survival of patients with IAGC[35,36]. In the future, high-quality multicenter clinical RCTs evaluating the effect of gastrectomy on OS are warranted.

Conclusions

The above results suggested that PG plus chemotherapy may provide a survival benefit compared with non-resection surgery plus chemotherapy in IAGC patients requiring surgical intervention. However, further prospective trials and RCTs are required to validate the survival benefits of PG plus chemotherapy in patients with IAGC requiring surgical intervention.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Informed Consent

As this was a retrospective study, formal consent was not required.

Ethical Approval

All procedures followed were in accordance with the ethical standards of the Responsible Committee on Human Experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions.

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