



ORIGINAL ARTICLE

# The long-term prognostic difference between gastrectomy with and without preoperative chemotherapy in patients with clinical stage IV gastric cancer



Ji-Hyeon Park <sup>a</sup>, Jun-Young Yang <sup>b,\*</sup>, Yeon-Ho Park <sup>b</sup>,  
Woon-Kee Lee <sup>b,\*\*</sup>

<sup>a</sup> Department of Surgery, Gachon University Gil Medical Center, 21 Namdong-daero 774 Beon-gil, Namdong-gu, Incheon, 21565, Republic of Korea

<sup>b</sup> Department of Surgery, Gachon University College of Medicine, Hambacwero 191, Yeonsu-gu, Incheon, 21936, Republic of Korea

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## KEYWORDS

Carcinomatosis;  
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**Summary** *Background/objective:* The role of gastrectomy for stage IV gastric cancer (GC) has not yet been established. Thus, we aimed to compare the prognoses of patients with clinical stage IV GC who underwent gastrectomy with and without preoperative chemotherapy after precise recategorization of patients.

*Methods:* We retrospectively reviewed a total of 92 clinical stage IV GC patients who underwent gastrectomy with or without preoperative chemotherapy between 2010 and 2016 at a single institution. Yoshida's classification was used to categorize the patients into the following categories: 1, technically resectable metastasis; 2, marginally resectable metastasis; 3, unresectable peritoneal dissemination; and 4, incurable peritoneal dissemination with distant organ metastasis. Two-year disease-specific survival (DSS) rates were compared between patients who underwent primary surgery and preoperative chemotherapy for each category.

*Results:* The two-year DSS rates of primary surgery vs. preoperative chemotherapy in Categories 1, 2, 3, and 4 ( $n = 35, 39, 14,$  and  $4,$  respectively) were 48.6% vs. 41.7% ( $p = 0.829$ ), 52.6% vs. 40.0% ( $p = 0.855$ ), 50.0% vs. 75.0% ( $p = 0.027$ ), and 0% vs. 66.7% ( $p = 0.083$ ), respectively. Patients in Categories 1 and 2 who underwent preoperative chemotherapy tended to have lower two-year DSS rates ( $p = 0.911$ ), whereas patients in Categories 3 and 4 had significantly higher two-year DSS rates than those who underwent primary surgery ( $p = 0.014$ ).

\* Corresponding author. Fax: +82 32 460 3247.

\*\* Corresponding author.

E-mail addresses: [glmt2100@gmail.com](mailto:glmt2100@gmail.com) (J.-Y. Yang), [lwk@gilhospital.com](mailto:lwk@gilhospital.com) (W.-K. Lee).

**Conclusions:** Primary surgery may be performed in patients without peritoneal dissemination when GC is technically resectable. However, if peritoneal dissemination is suspected, chemotherapy should be prioritized.

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## 1. Introduction

Systemic chemotherapy is generally prioritized for patients with clinical stage IV gastric cancer (GC) because primary gastrectomy in the absence of chemotherapy is generally thought to yield poor outcomes in this population. However, patients with stage IV GC have a life expectancy of only 10–13 months, even with systemic chemotherapy.<sup>1–3</sup> Therefore, recent studies have focused on finding more effective treatments for patients with stage IV GC.

One of the recent emerging concepts is “conversion surgery”. Among clinically unresectable stage IV GC cases, some with a good chemotherapy response could be converted into resectable cases with curative intent during chemotherapy, and a significant improvement in survival rate has been reported in many studies.<sup>4,5</sup>

However, patients with stage IV GC exhibit heterogeneous disease courses due to differences in the degree of severity. Therefore, an appropriate reclassification of patients with stage IV GC is needed to individualize the treatments. Yoshida et al reclassified stage IV GC into four categories, namely potentially resectable metastasis, marginally resectable metastasis, peritoneal dissemination without distant metastasis, and peritoneal dissemination with distant metastasis.<sup>6</sup>

Thus, this study aimed to recategorize patients with clinical stage IV GC and to identify effective treatments for each category by comparing the long-term prognoses between gastrectomy with and without preoperative chemotherapy.

## 2. Methods

### 2.1. Patients

Of the 1880 patients who underwent surgery for GC between 2010 and 2016 at Gachon University Gil Medical Center, we first excluded those with clinical stage I, II, or III GC (Fig. 1). All cases of GC were confirmed by preoperative gastrofibroscopy (GFS) biopsy. Regional cancer invasion and metastasis were confirmed by preoperative computed tomography (CT). Distant metastasis and peritoneal dissemination were confirmed by magnetic resonance imaging (MRI), whole-body positron emission tomography-computed tomography (PET-CT), staging laparoscopy, or laparotomy. Finally, data from 175 patients diagnosed with clinical stage IV GC were reviewed retrospectively. Among them, 83 patients who received chemotherapy only after palliative surgery (e.g., gastric bypass, open and closure, and staging laparoscopy) were excluded. The remaining 92 clinical stage IV GC patients underwent gastrectomy with D2 lymph node (LN) dissection. Metastatic lesions were resected as far as possible with curative intent. Forty-four patients underwent

chemotherapy followed by gastrectomy according to the response to chemotherapy, whereas the remaining 48 patients underwent primary gastrectomy without preoperative chemotherapy. Pathologic stage was classified according to the American Joint Committee on Cancer (seventh edition).<sup>7</sup> All procedures were conducted in accordance with the ethical standards of the respective institutional and national committees on human experimentation and with the 1964 and later versions of the Declaration of Helsinki. The study was approved by the Institutional Review Board of Gachon University (IRB No. GFIRB2018-171).

### 2.2. Clinical stage IV classification according to Yoshida’s classification

The 92 patients were re-classified according to Yoshida’s new classification<sup>8</sup> for stage IV GC. Patients were first divided into two groups according to the presence or absence of peritoneal dissemination: Category 1/2 and Category 3/4, respectively. These two groups were then each divided to yield four groups according to the degree of metastasis. Category 1 was defined as the presence of a technically resectable metastasis, such as a single liver metastasis or no. 16a2 and/or 16b1 paraaortic LN metastasis. Category 2 was defined as a marginally resectable metastasis, such as multiple liver metastases or distant LN metastasis. Category 3 was defined as peritoneal dissemination without any other organ metastasis. Category 4 included peritoneal dissemination with metastasis to other organs.

### 2.3. Indication for surgery after preoperative chemotherapy

Forty-four patients received at least one cycle of preoperative chemotherapy (average: 4–6 cycles) before gastrectomy; the regimens differed among patients. The timing of surgery differed among the patients as the

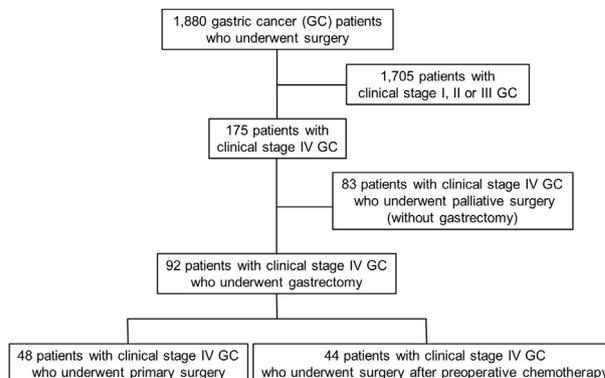


Figure 1 Flow chart.

procedures were performed when a R0 resection was deemed possible. Chemotherapy responses were classified during follow-up according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines.<sup>9</sup> Surgery after preoperative chemotherapy was performed in patients who achieved partial remission or complete remission during different chemotherapy periods. Regular GFS and CT scans were performed every three months; other radiological modalities such as MRI and PET-CT were used if necessary. All cases were subjected to multidisciplinary assessments to determine the best timing for surgery.

## 2.4. Indication for primary surgery

A total of 48 patients underwent primary gastrectomy without preoperative chemotherapy for the following

reasons: i) the patient desired surgery before chemotherapy, ii) the surgeon decided that R0 resection might be possible at the time of diagnostic laparoscopy or laparotomy, iii) the patient's general condition was not sufficient for chemotherapy (e.g., old age), and iv) serious complications such as obstruction, bleeding, perforation, or severe cancer-related symptoms were present.

## 2.5. Postoperative chemotherapy

Regardless of their preoperative chemotherapy status, postoperative chemotherapy was planned for all patients with pathological stage II or higher, except for patients with poor general status (e.g., old age, comorbidity, postoperative complications) or in cases of the patient's refusal to undergo postoperative chemotherapy.

**Table 1** Patient characteristics.

	Primary surgery <i>n</i> = 48 (%)	Surgery after preoperative chemotherapy <i>n</i> = 44 (%)	<i>P</i> -value
Age	64.5 ± 12.3	61.7 ± 10.0	0.248
Gender			0.826
Male	38 (79.2)	34 (77.3)	
Female	10 (20.8)	10 (22.7)	
BMI	22.0 ± 3.6	22.6 ± 3.8	0.390
Comorbidities <sup>a</sup>			0.229
0	24 (50.0)	18 (40.9)	
≥1	21 (43.8)	20 (45.5)	
≥3	3 (6.3)	6 (13.6)	
Previous abdomen operation history			0.449
No	42 (87.5)	36 (81.8)	
Yes	6 (12.5)	8 (18.2)	
ASA score			0.338
1	8 (16.7)	2 (4.5)	
2	36 (75.0)	40 (90.9)	
3	4 (8.3)	2 (4.5)	
Initial incurable factor <sup>b</sup>			0.021
Category 1	23 (47.9)	12 (27.3)	
Category 2	19 (39.6)	20 (45.5)	
Category 3	5 (10.4)	9 (20.5)	
Category 4	1 (2.1)	3 (6.8)	
Preoperative chemotherapy response			
PR		40 (90.9)	
CR		4 (9.09)	
Postoperative chemotherapy			0.820
No	13 (27.1)	11 (25.0)	
Yes	35 (72.9)	33 (75.0)	

Values are presented as mean ± standard deviation or number (%).

BMI: Body mass index.

ASA score: American Society of Anesthesiologist score.

PR: Partial remission.

CR: Complete remission.

<sup>a</sup> HTN, DM, CKD, Athsma, COPD, CAOD, etc.

<sup>b</sup> Incurable factor.

Category 1: Peritoneal dissemination (–), potentially resectable metastasis, resectable single liver metastasis, few paraaortic LN metastasis.

Category 2: Peritoneal dissemination (–), marginally resectable metastasis, multiple liver metastasis, distant organ metastasis, multiple paraortic LN and distant LN metastasis.

Category 3: Peritoneal dissemination (+), distance organ metastasis (–).

Category 4: Peritoneal dissemination (+), distance organ metastasis (+).

**Table 2** Operative and pathologic result.

	Primary surgery <i>n</i> = 48 (%)	Surgery after preoperative chemotherapy <i>n</i> = 44 (%)	<i>P</i> -value
Operation name			0.548
Distal gastrectomy	27 (56.3)	22 (50.0)	
Total gastrectomy	21 (43.8)	22 (50.0)	
Extended resection			0.606
None	33 (68.8)	31 (70.5)	
Spleen	5 (10.4)	6 (13.6)	
Small intestine	0 (0)	1 (2.3)	
Large intestine	3 (6.3)	0 (0)	
More than two organs	7 (14.6)	6 (13.6)	
Tumor size (cm)	7.8 ± 2.9	5.9 ± 3.4	0.005
Tumor invasion			0.000
T0	0 (0)	3 (6.8)	
T1	0 (0)	4 (9.1)	
T2	1 (2.1)	5 (11.4)	
T3	12 (25.0)	15 (34.1)	
T4	35 (72.9)	17 (38.6)	
Nodal metastasis			0.001
N0	1 (2.1)	12 (27.3)	
N1	6 (12.5)	6 (13.6)	
N2	9 (18.8)	9 (20.5)	
N3	32 (66.7)	17 (38.6)	
Total number of harvested LN	37.0 ± 14.6	32.9 ± 18.0	0.234
Number of positive LN	14.5 ± 12.7	7.2 ± 10.0	0.003
Distant metastasis (Pathologically confirmed)			0.002
No	23 (47.9)	35 (79.5)	
Yes	25 (52.1)	9 (20.5)	
Final pathologic stage			0.000
I	0 (0)	6 (13.6)	
II	0 (0)	5 (11.4)	
III	23 (47.9)	24 (54.5)	
IV	25 (52.1)	9 (20.5)	

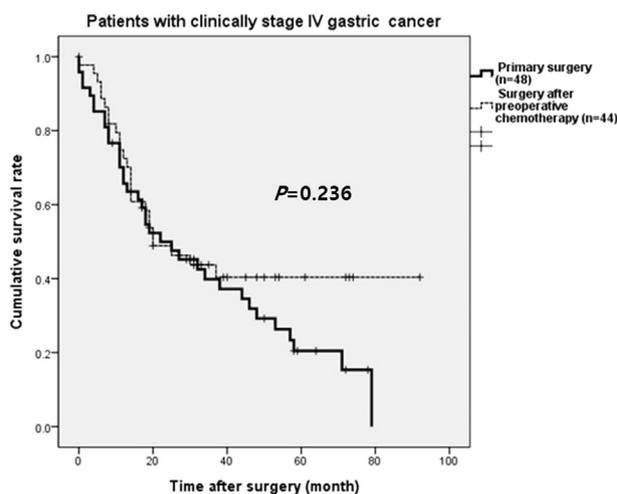
Values are presented as mean ± standard deviation or number (%).  
LN: Lymph node.

## 2.6. Statistics

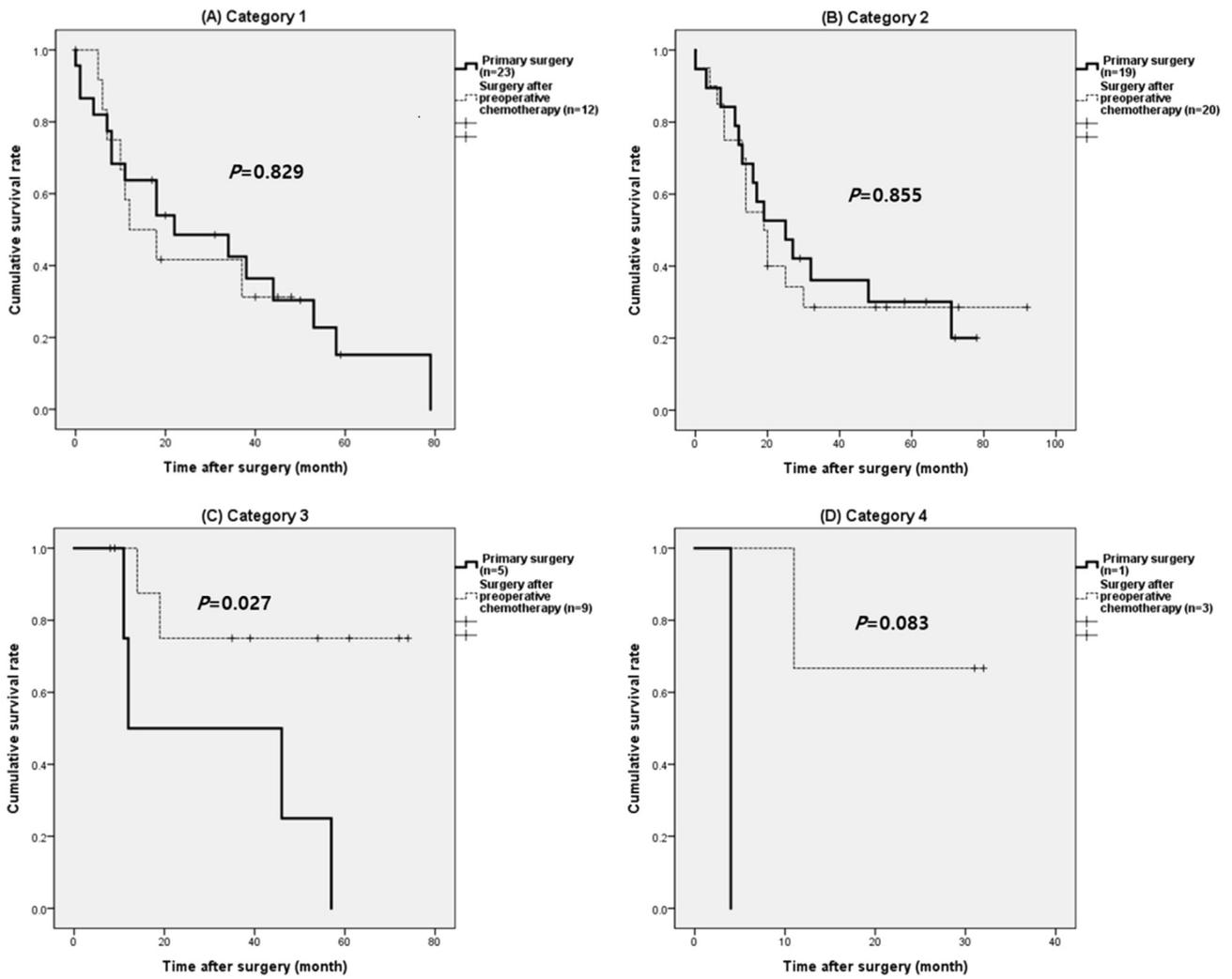
The clinicopathological characteristics and surgical results of the two groups were compared using the chi-square test, Fisher's exact probability test, a linear-by-linear association analysis, or independent sample T-test, as appropriate. Continuous variables are presented as medians and ranges. Disease-specific survival (DSS) rates were calculated from the date of surgery to the date of death due to GC or the latest follow-up date. DSS was calculated using a Kaplan–Meier curve analysis and was compared using the log-rank test. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 23.0 (IBM Co., Armonk, NY, USA). Two-sided *p*-values of <0.05 were considered statistically significant.

## 3. Results

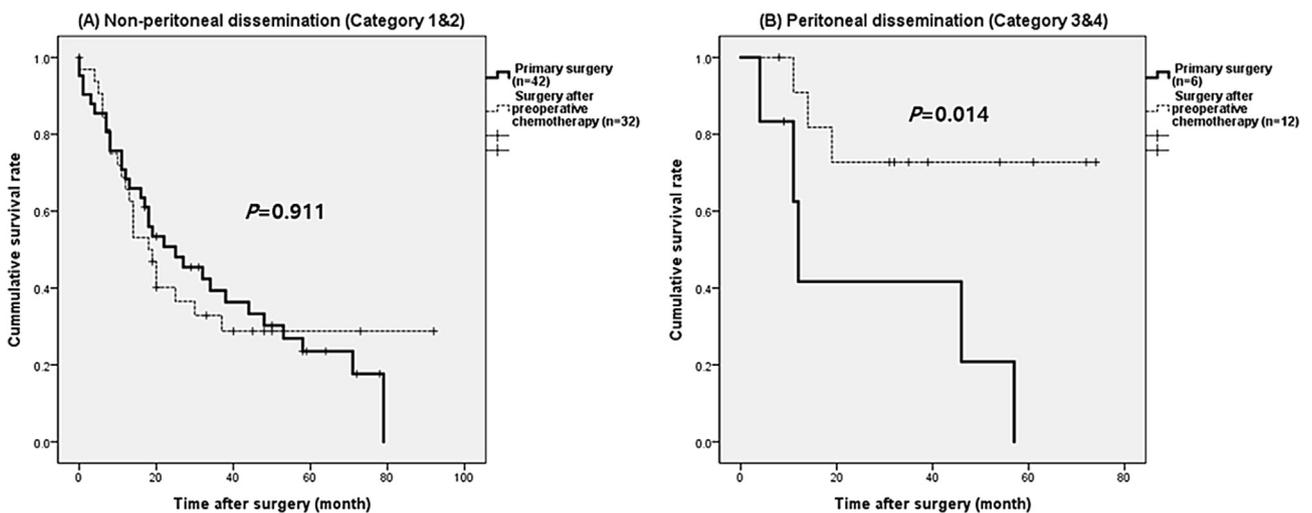
The patients' characteristics are listed in Table 1. There were no significant differences between the primary surgery and preoperative chemotherapy groups other than the



**Figure 2** Disease specific survival rate between primary surgery and conversion surgery. (\**n*: Number of patients).



**Figure 3** Disease specific survival rate according to Yoshida's classification (A) Category 1, (B) Category 2, (C) Category 3 and (D) Category 4. (\*n: Number of patients).



**Figure 4** Disease specific survival rate according to presence or absence of peritoneal dissemination (A) Non-peritoneal dissemination and (B) Peritoneal dissemination. (\*n: Number of patients).

initial incurable factors. When the patients were further divided into four categories according to these initial incurable factors, Category 1 (technically resectable metastasis) was the most common among patients who underwent primary gastrectomy (23 patients, 47.9%), and Category 2 (technically unresectable metastasis) was the most common among those who underwent surgery after preoperative chemotherapy (20 patients, 45.5%) ( $p = 0.021$ ). Based on imaging studies, 90% of patients in the preoperative chemotherapy group showed partial remission, and 10% of patients showed complete remission.

Table 2 describes the patients' operative and pathologic outcomes. There was no significant inter-group difference in the operative results. However, the pathologic outcomes were significantly different between the two groups. The preoperative chemotherapy group showed a significant decrease in pathologic stage compared to the primary surgery group. The average tumor size was significantly smaller in the preoperative chemotherapy group than in the primary gastrectomy group ( $p = 0.005$ ). Regarding T staging, T4 was significantly more common in the primary gastrectomy group, whereas T0–T3 were more common in the preoperative chemotherapy group ( $p = 0.000$ ). Regarding N staging, although N3 accounted for the largest proportion of patients in both groups, more than half of patients in the primary surgery group met this category, whereas more than half of patients in the preoperative chemotherapy group were classified as N0–N2 ( $p = 0.001$ ). There was no significant difference in the total number of harvested LNs between the groups (37.0 vs. 32.9,  $p = 0.234$ ). However, a significantly smaller number of positive LNs was observed in the preoperative chemotherapy group (14.5 vs. 7.2,  $p = 0.003$ ). Furthermore, significantly fewer distant metastases were observed in the preoperative chemotherapy group relative to the primary surgery group ( $p = 0.002$ ). Regarding the final pathological staging, even though 75% of cases in the preoperative chemotherapy group were still classified as high stage (i.e., stage 3 and 4), 25% of the group showed lower pathological stages (i.e., stage 1 and 2;  $p = 0.000$ ), which is a statistically significant difference.

No significant differences in postoperative complications were observed between the groups (Supplementary Table 1). The primary surgery group tended to have more severe complications than the preoperative chemotherapy group when the complications were categorized according to the Clavien–Dindo classification; however, this difference was not statistically significant.<sup>10</sup> Major complications in the primary surgery group included intra-abdominal abscess, bleeding, and sepsis, whereas superior mesenteric artery infarction, anastomosis leakage, and hepatic failure were observed in the preoperative chemotherapy group.

The primary and preoperative chemotherapy groups had two-year DSS rates of 49.9% and 48.9%, respectively, but this difference was not statistically significant (Fig. 2,  $p = 0.236$ ). When the patients were divided into four categories according to Yoshida's classification, the two-year DSS rates of patients who underwent primary vs. preoperative chemotherapy were 48.6% vs. 41.7% (Fig. 3A,  $p = 0.829$ ) for Category 1, 52.6% vs. 40.0% (Fig. 3B,  $p = 0.855$ ) for Category 2, 50.0% vs. 75.0% (Fig. 3C,  $p = 0.027$ ) for Category 3, and 0% vs. 66.7% (Fig. 3D,  $p = 0.083$ ) for Category 4. Survival was analyzed according

to peritoneal dissemination (Fig. 4). The two-year DSS rates of patients in the primary and preoperative chemotherapy groups were 50.7% and 40.2%, respectively, for patients without peritoneal dissemination (Fig. 4A,  $p = 0.911$ ), and 41.7% and 72.7%, respectively, for those with peritoneal dissemination (Fig. 4B,  $p = 0.014$ ).

#### 4. Discussion

Stage IV GC is especially heterogeneous. The presence of distant metastasis automatically classifies a patient as having clinical stage IV GC, although the clinical T and N stages may not reflect this classification. However, survival may be affected by the degree of metastasis or other features.<sup>11</sup> Therefore, new classifications of stage IV GC should be considered. As noted, the present study used Yoshida's classification for stage IV GC.<sup>8</sup> According to our findings, patients with technically resectable metastasis were classified into Category 1, and primary gastrectomy was possible for many such patients. However, chemotherapy was more frequently administered first to patients in Categories 2, 3, and 4. In Yoshida's study, all clinical stage IV GC patients underwent initial chemotherapy after which specifically selected patients underwent conversion surgery: the treatment strategy is converted by chemotherapy to curative surgery. Therefore, patients with technically resectable metastasis without peritoneal dissemination (Category 1) were considered for neoadjuvant chemotherapy. The patients in the neoadjuvant chemotherapy group survived for a mean of 20 months longer than did those in the chemotherapy-only group.<sup>1</sup> In our study, Category 1 patients in the primary surgery group tended to have a better prognosis than did those in the preoperative chemotherapy group, although this difference was not statistically significant. This result suggests that if the primary and metastatic tumors are technically resectable, primary surgery can be considered for patients in Category 1.

Patients for whom R0 resection was impossible were classified as Category 2, 3, or 4. Chemotherapy is usually prioritized for these categories. In our study, we observed that the frequency of surgery after preoperative chemotherapy relative to primary surgery increased as the Yoshida category number increased. Surgery after preoperative chemotherapy is considered a therapeutic strategy for patients with stage IV GC who may be able to achieve an R0 resection after effective chemotherapy.<sup>2</sup> Conversion surgery has been studied extensively. However, previous studies have usually compared chemotherapy-only and conversion surgery groups, and, thus, it is difficult to compare the actual pathological results.<sup>12</sup> As all patients in our study underwent gastrectomy with D2 LN dissection, we were able to compare the pathological results between the groups. Our results demonstrated better pathological results with surgery after preoperative chemotherapy in patients with good chemotherapy responses. Although all patients in both groups were initially suspected to have clinical stage IV disease, patients in the preoperative chemotherapy group had lower pathological T, N, and M stages than those in the primary surgery group. Therefore, it is important to monitor responses to chemotherapy and

to make careful decisions regarding conversion surgery for patients in Categories 2, 3, and 4.

Kim et al reported a better prognosis with gastrectomy relative to palliative gastric surgery (e.g., bypass) or exploration in stage IV patients, except for those with peritoneal dissemination.<sup>13</sup> Measurable lesions with hematologic metastasis can be surgically removed if the process is technically feasible. However, the complete removal of peritoneal dissemination is highly challenging as the lesion has theoretically disseminated throughout the abdominal cavity.<sup>14</sup> Therefore, it is important to identify patients with a relatively good prognosis as those who would most benefit from aggressive surgery. In our analysis of patients with peritoneal dissemination (Categories 3 and 4), those who underwent surgery after preoperative chemotherapy tended to have a better two-year DSS rate than those who underwent primary surgery. Patients with peritoneal dissemination who responded well to preoperative chemotherapy also had better two-year DSS rates. Furthermore, many studies have shown that patients with peritoneal dissemination usually respond well to chemotherapy.<sup>13,15</sup> Therefore, preoperative chemotherapy is prioritized in patients with clinical stage IV GC and peritoneal dissemination. However, if the patient responds well to chemotherapy, resection of the primary tumor and metastasis may be considered according to the optimal surgery timing.

This study had some limitations. First, liver/pelvic MRI or whole-body PET-CT, rather than staging laparoscopy or laparotomy, was used to confirm the presence of distant metastasis or peritoneal dissemination in some patients in the preoperative chemotherapy group. According to a previous meta-analysis, although preoperative CT scans can determine the GC stage with a relatively high level of accuracy (71% for T-staging, 66% for N-staging, and 81% for M-staging), diagnostic laparoscopy or laparotomy findings may be helpful if CT yields ambiguous results concerning peritoneal metastasis. Still, although staging laparoscopy is associated with a lower 30-day mortality rate and a shorter length of hospital stay relative to (open) laparotomy, it is an invasive means of confirming the clinical stage. Therefore, endoscopic ultrasound, MRI, or PET may be indicated to answer specific questions regarding the CT findings.<sup>16,17</sup> The efficacy of surgery after preoperative chemotherapy in patients with clinical stage IV GC remains controversial. Therefore, diagnostic laparoscopy was not performed in some of the retrospective studies when the patients were classified as clinical stage IV GC because it was not possible to determine which patients were able to undergo conversion surgery due to a good response to chemotherapy at the time of the diagnosis.<sup>18,19</sup> The patients included in our study were strongly suspected to have clinical stage IV GC following a preoperative examination, and surgery after preoperative chemotherapy was not expected at the time of the initial diagnosis. Therefore, further non-invasive imaging methods were used to confirm clinical stage IV GC, rather than burden the patients with an invasive procedure under general anesthesia.

Second, this study was designed for patients with clinical rather than pathological stage IV GC, because a treatment decision is usually made at the time of initial clinical diagnosis. In our study, 48% of the patients in the primary surgery group showed pathological stage III GC. However,

these patients were strongly suspected to have stage IV GC even in the surgical field, considering their severe tumor burden and distant lymph nodes and/or other organ metastasis. Therefore, some of the metastatic lesions were not always resected due to a decision by the surgeon based on the individual circumstances. Even though these cases were described as stage III on the pathologic reports because of the unavailability of metastatic specimen for pathological confirmation, it is likely that these patients were actually stage IV patients. The same condition was applied to the preoperative chemotherapy group since they received chemotherapy first without any pathological confirmation. This limitation is the result of the retrospective nature of our study.

The REGATTA trial compared gastrectomy plus chemotherapy with chemotherapy alone in patients with advanced GC with a single non-curable factor.<sup>20</sup> Yoshida et al re-classified patients with clinical stage IV GC into four groups for a comparison of chemotherapy alone with conversion surgery in this population.<sup>1,6</sup> Despite the limitations of our study and its single-institution retrospective design, our findings are meaningful because this was the first study to use these methods to re-classify patients with stage IV GC and, subsequently, compare the outcomes of gastrectomy with or without preoperative chemotherapy. However, prospective multi-center studies of this topic are needed to generalize our hypothesis.

In conclusion, both the re-classification of patients with stage IV GC and the identification of appropriate treatments for each group are essential to improve survival rates in this patient population. A more precise classification of stage IV GC could enable a more active application of primary gastrectomy to patients with technically resectable disease in the absence of peritoneal dissemination. However, patients with clinically suspected peritoneal dissemination may achieve a better prognosis with preoperative chemotherapy and an optimally timed surgery after preoperative chemotherapy, rather than primary surgery.

## Declaration of interest

None.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.asjsur.2019.01.006>.

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