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Prognostic factors of conversion surgery for stage IV gastric cancer: A multi-institutional retrospective analysis

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Abstract

Background: Conversion surgery (CS) is a highly anticipated strategy for stage IV advanced gastric cancer (AGC) with a good response to chemotherapy. However, prognostic factors limiting R0 resection remain unclear. In this multi-institutional study, we investigated the clinical outcomes of CS for stage IV AGC and the prognostic factors of CS-limiting R0 resection and analyzed them according to metastatic patterns.

Methods: Clinical data on 210 patients who underwent CS for stage IV AGC at six institutions between 2007 and 2017 were retrospectively retrieved. The patient background, preoperative treatment, operative outcomes, and survival times were recorded. Prognostic factors for overall and recurrence-free survival were investigated using univariate and multivariate analyses for patients who underwent R0 resection.

Results: R0 resection was achieved in 146 (70%) patients. The median survival time was 32 months, and the 3-year survival rate was 45%. Patients who achieved R0 resection had significantly longer survival than those with R1/2 resection (median survival time: 41.5 months vs. 20.7 months). Multivariate analysis identified pathological N positivity for overall and relapse-free survival and pathological T4 for relapse-free survival as significant independent poor prognostic factors of R0 resected patients. There was no significant difference in survival among the peritoneum, liver, and lymph node groups regarding the initial metastatic sites.

Conclusions: CS with R0 resection for patients with stage IV AGC can lead to longer survival. Patients with pathological T4 and pathological N positivity were eligible for intensive adjuvant therapy after CS with R0 resection.

KEYWORDS
conversion surgery, gastric cancer, prognostic factor, R0 resection, stage IV

1 | INTRODUCTION

Gastric cancer remains one of the most common causes of cancer-related deaths worldwide, despite a remarkably improved survival trend through early detection and curative surgery. Advanced gastric cancer (AGC) with distant metastasis is categorized as stage IV and has no indications for curative surgical resection except for palliation. Although recent advances in chemotherapy have resulted in considerable tumor shrinkage in many AGC cases, these treatments have not resulted in a cure. The median survival time (MST) reached in various clinical trials for the disease at this stage remains at 6–14 months.[1,2] The current purpose of chemotherapy for stage IV AGC is to prolong survival as long as possible by delaying or relieving the cancer-related symptoms.

Surgery for stage IV AGC is considered non-curative and is classified as palliative or reduction surgery, depending on the aim of the surgery. An international cooperative randomized controlled trial (REGATTA, JCOG0705/KGCA01) failed to demonstrate the survival benefit of reduction surgery.[3] Therefore, according to the 2018 Japanese Gastric Cancer Treatment Guidelines (5th edition), surgeons are strongly advised not to perform this type of surgery.[4] On the other hand, conversion surgery (CS) as a new therapeutic strategy has been proposed for patients with stage IV AGC who achieved good chemotherapy response aiming for long-term survival.[5] Although most studies reporting treatment outcomes of CS are retrospective, better long-term outcomes have been reported in patients who responded to chemotherapy or achieved R0 resection.[6-10]

Previous studies on CS, including the CONVO-GC-1 study,[10] have usually included cases of non-curative resection because of the insufficient number of target cases. However, assuming that only patients with R0 resection can benefit from survival is reasonable. No report was limited to R0 resection cases of CS, and a prognostic analysis for R0 resected cases has never been studied. In addition, the survival analysis for each metastatic site in R0 cases with a single metastasis has yet to be elucidated. These analyses may be useful for improving the prognosis of CS.

In this retrospective study, we first evaluated the clinical outcome of CS in 210 patients with stage IV AGC treated between 2007 and 2017 at six institutions and analyzed the prognostic factors of CS only in the 146 R0 resected cases. Second, we performed survival analysis for each metastatic site in R0 cases with a single metastasis.

2 | METHODS

2.1 | Patients and data retrieval

Between 2007 and 2017, 213 patients with stage IV AGC underwent CS at six institutions (Osaka National Hospital, Osaka General Medical Center, Osaka Police Hospital, Osaka International Cancer Institute, Kansai Rosai Hospital, and Osaka University Hospital).

Three patients who underwent palliative surgery were excluded. Thus, the clinical data of 210 patients were retrieved and analyzed in this study. The following parameters were collected and analyzed: sex, age, histological type, cT, cN, cM, cStaging (according to the 8th edition of the Union for International Cancer Control [UICC] TNM Classification of Malignant Tumors), line of chemotherapy, and duration of chemotherapy. Stage IV disease was stratified according to a new classification proposed by Yoshida et al.[5] as follows. Category 1 included tumors that were technically resectable, such as solitary liver metastasis (up to 5 cm), para-aortic lymph node (LN) metastasis localized in station No. 16a2/b1, or peritoneal lavage cytology-positive disease without macroscopic peritoneal dissemination. Category 2 included tumors with marginally resectable or unresectable metastasis such as solitary liver metastasis larger than 5 cm, multiple liver metastases, or distant LN metastasis other than para-aortic LN No 16a2/b1 but without apparent peritoneal disease. Category 3 included tumors with peritoneal dissemination without any other distant metastasis. Category 4 included tumors with peritoneal dissemination accompanied by another distant metastasis. Surgical data, including surgical approach, type of gastrectomy, R status, and metastasectomy, were also analyzed. Surgical outcomes and complications were assessed. Various complications such as anastomotic leakage, pancreatic fistula, and abdominal abscess were diagnosed radiographically and clinically and graded according to the Clavien–Dindo classification.[11] Data on pathological TNM stage, histological response, and adjuvant chemotherapy were collected.

2.2 | Analysis of prognostic factors for survival

Survival time was defined as the time from the start of treatment to death. Univariate analysis assessed the association between each clinicopathological factor and overall survival (OS) and relapse-free survival (RFS). Multivariate analysis was also performed to identify variables that were independently associated with both OS and RFS.

2.3 | Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics Version 28 (IBM Corporation, Armonk, NY, USA). Differences were analyzed for statistical significance using the chi-square test for categorical variables and Student's t-test for continuous variables. OS analysis was performed using Kaplan–Meier curves. Independent prognostic factors were identified through multivariate analysis using the Cox regression hazard model. Independent risk factors were analyzed using multivariate analysis with multiple logistic regression. If a variable remained statistically significant at a level of $p < 0.2$ in the univariate analysis, it was incorporated into the final multivariate model. Differences were considered statistically significant at $p < 0.05$.

3　|　RESULTS

3.1　|　Patients' characteristics

The clinical characteristics of the 210 patients are summarized in Table 1. They consisted of 150 (71%) males and 60 (29%) females, with a median age of 64 (25–84) years. The main cause of unresectability was the presence of distant LN metastases in 85 (40%) patients. Other causes included peritoneal dissemination (P1) in 58 (28%) patients, cytological positive findings (P0CY1) in 53 (25%) patients, and liver metastases in 42 (20%) patients. Cytological tests were not performed for 51 (24%) patients. The number of patients in categories 1, 2, 3, and 4 were 108 (51%), 44 (21%), 46 (22%), and 12 (6%), respectively. As induction chemotherapy, triplet regimens were selected in 35 (17%) patients, and doublet regimens were selected in 144 (69%) patients. HER2-positive gastric cancer was found in 21 (10%) patients who underwent trastuzumab-based chemotherapy. Intraperitoneal chemotherapy was administered in 30 (14%) patients. Second-line chemotherapy was administered to 17 (8%) patients. The median duration of chemotherapy was 3.2 (0.7–34.9) months. The median follow-up time was 31 (3.4–174.7) months.

3.2　|　Surgical outcomes and postoperative complications

Surgical outcomes are summarized in Table 1. Most CS (77%) were performed by open surgery. The types of gastrectomies were divided into 125 (60%) total gastrectomies, 73 (35%) distal gastrectomies, and 12 (5%) proximal gastrectomies. R0 resection was achieved in 146 (70%) patients. Metastasectomies were performed in 62 (30%) patients.

TABLE 1　Characteristics and surgical and pathological outcomes of patients.

	$n = 210$ (%)
Age median (year)	64 (25–84)
Sex (male/female)	150 (71)/60 (29)
Histological type (differentiated/undifferentiated)	88 (42)/122 (58)
cT (1/2/3/4a/4b)	1 (0.4)/3 (1.4)/52 (25)/140 (67)/14 (7)
cN (0/1/2/3)	34 (16)/58 (28)/72 (34)/46 (22)
Cytology positive (P0CY1)	53 (25)
Peritoneal metastasis (P1)	58 (28)
Hepatic metastasis (H1)	42 (20)
Distant LN metastasis (M1LYM)	85 (40)
Yoshida category (1/2/3/4)	108 (51)/44 (21)/46 (22)/12 (6)
Induction chemotherapy (first line/second line)	193 (92)/17 (8)
Median duration of chemotherapy (months)	3.2 (0.7–34.9)
Preoperative staging laparoscopy	122 (58)
Approach (Open/Lap)	162 (77)/48 (23)
Type of gastrectomy (DG/PG/TG)	73 (35)/12 (5)/125 (60)
R0/R1/R2	146 (70)/34 (16)/30 (14)
Metastasectomy (y/n)	62 (30)/148 (70)
Postoperative complication	
Clavien–Dindo grade ≥II	39 (18.5)
pT (0/1/2/3/4a/4b)	15 (7)/19 (9)/11 (5)/82 (39)/67 (32)/16 (8)
pN (0/1/2/3)	58 (28)/32 (15)/36 (17)/84 (40)
pM (0/1)	118 (56)/92 (44)
Pathological cytology positive (CY1)	36 (17)
Pathological peritoneal metastasis (P1)	24 (11)
Pathological hepatic metastasis (H1)	20 (9)
Pathological distant LN metastasis (M1LYM)	25 (12)
Pathological response (Grade 0/1a/1b/2/3/NA)	10 (5)/108 (51)/34 (16)/37 (18)/15 (7)/6 (3)

Note: Data are presented as _n_ (%) or median (interquartile range).

Abbreviations: DG, distal gastrectomy; Lap, laparoscopy; LN, lymph node; NA, not applicable; PG, proximal gastrectomy; TG, total gastrectomy.

The postoperative complications after CS are shown in Table 1. The number of patients who presented with Clavien–Dindo grade ≥II and ≥III was 39 (18.5%) and 16 (7.6%), respectively. These included surgical complications such as abdominal abscess ($n = 23$, 10.9%), surgical site infection ($n = 9$, 4.2%), pancreatic fistula ($n = 7$, 3.3%), anastomotic leakage ($n = 3$, 1.4%), bleeding ($n = 1$, 0.4%), and non-surgical complications ($n = 4$, 1.9%). No mortality was related to surgery.

After R0 resection, adjuvant chemotherapy was administered to 119 (82%) patients. Eighty-two (69%) patients received S1 monotherapy, and the preoperative regimens were continued in the remaining patients. Fifty-three (45%) patients terminated the adjuvant therapy due to recurrence.

3.3 | Pathological variables

Pathological variables are also shown in Table 1. Final pM1 occurred in 92 (44%) cases, including CY1 (17%), P1 (11%), H1 (9%), and M1LYM (12%). The pathological response was Grade 0 (10 [5%]), Grade 1a (108 [51%]), Grade 1b (34 [16%]), Grade 2 (37 [18%]), and Grade 3 (15 [7%]).

3.4 | Survival analysis

The median OS was 32 [95% confidence interval 26.1–38.0] months, and the 3-year survival rate was 45%. Patients who achieved R0 resection had significantly longer survival than patients who underwent R1/2 resection (MST: 41.5 [32.4–51.5] months vs. 20.7 [14.4–26.9] months; $p < 0.001$, log-rank test) (Figure 1A). The MST in each category was 28.9 [22.0–36.5] months in category 1, 37.5 [20–63.1] months in category 2, 36 [28.1–47.6] months in category 3, and 15.1 [4.1–26.0] months in category 4 (Figure 1B).

3.5 | Prognostic factor analysis

Univariate analysis of OS limited to only the 146 patients who achieved R0 resection showed that pathological T4, pathological N, and pathological effect Grade 0–2 were significantly correlated with poor prognosis (Table 2). The Cox proportional hazards regression model identified pathological N positivity as a significant independent prognostic factor of OS using eight variables which remained statistically significant at a level of $p < 0.2$ in the univariate analysis (Table 2). Figure 1C shows the OS curves according to pN status. Moreover, univariate analysis of RFS showed that several non-curative factors, pathological T4, pathological N, and pathological effect Grade 0–2 were significantly correlated with poor prognosis (Table 3). The Cox proportional hazards regression model identified pathological T4 and pathological N positivity as significant independent prognostic factors of RFS using six variables which remained statistically significant at a level of $p < 0.2$ in the univariate

analysis (Table 3). Figures S1 show the RFS curves according to pT and pN status, respectively.

3.6 | Analysis of patients with a single non-curative factor

There were 132 patients with a single non-curative factor. The background characteristics of the 132 patients are summarized in Table 4. In total, 54 cases of peritoneal metastasis were identified, comprising 20 P0CY1 and 34 P1 cases. The peritoneal metastatic group included more patients with undifferentiated tumors, pT4, and those receiving adjuvant chemotherapy than the other two groups. The OS curves obtained by Kaplan–Meier analysis according to the three types of initial metastatic sites are shown in Figure 2. There was no significant difference among the three groups, and the 3-year survival rates for each type were 62.6% for liver metastasis, 52.3% for LN metastasis, and 56.9% for peritoneal metastasis. Eighty-three relapse cases occurred in 132 patients with a single non-curative factor. The overall pattern of relapse was 51% for the peritoneum, 33% for LNs, 17% for the liver, and 7% for other sites. Analysis of each site of initial metastasis showed that the relapse rates were 65% for the peritoneum, 76% for the liver, and 55% for the LNs. Accordant patterns of relapse with the site of initial metastasis were found in the peritoneum (89%), liver (58%), and LNs (62%) (Figure 3).

4 | DISCUSSION

In this retrospective study, we evaluated the clinical outcomes and prognostic factors of CS in 210 patients with stage IV AGC from six institutions. The results included identifying two prognostic factors, pathological T4 for RFS and pathological N positivity for OS and RFS, as significantly independent poor prognostic factors for patients with R0 resection. There was no significant survival difference between the three types of initial metastatic sites in the 132 patients with a single non-curative factor.

Although there is little doubt that surgical resection provides the only possible cure in patients with gastric cancer, stage IV AGC with advanced incurable disease is associated with a poor prognosis. The emergence of new anticancer drugs and highly effective regimens has resulted in remarkable tumor shrinkage. As a result, some patients with stage IV AGC who respond well to chemotherapy have undergone curative resection, followed by long-term survival. This concept, already suggested for treating colorectal liver metastases, has also been accepted as a "conversion surgery" for gastric cancer.

The general concept of oligometastatic cancer (OMC) was first introduced in 1995 and described a clinical state between locally confined and systemic metastatic disease.[12] The European group recently reached a consensus that the disease burden of one extra-regional LN station or one organ with three metastases could be considered OMC in esophagogastric cancer in the available
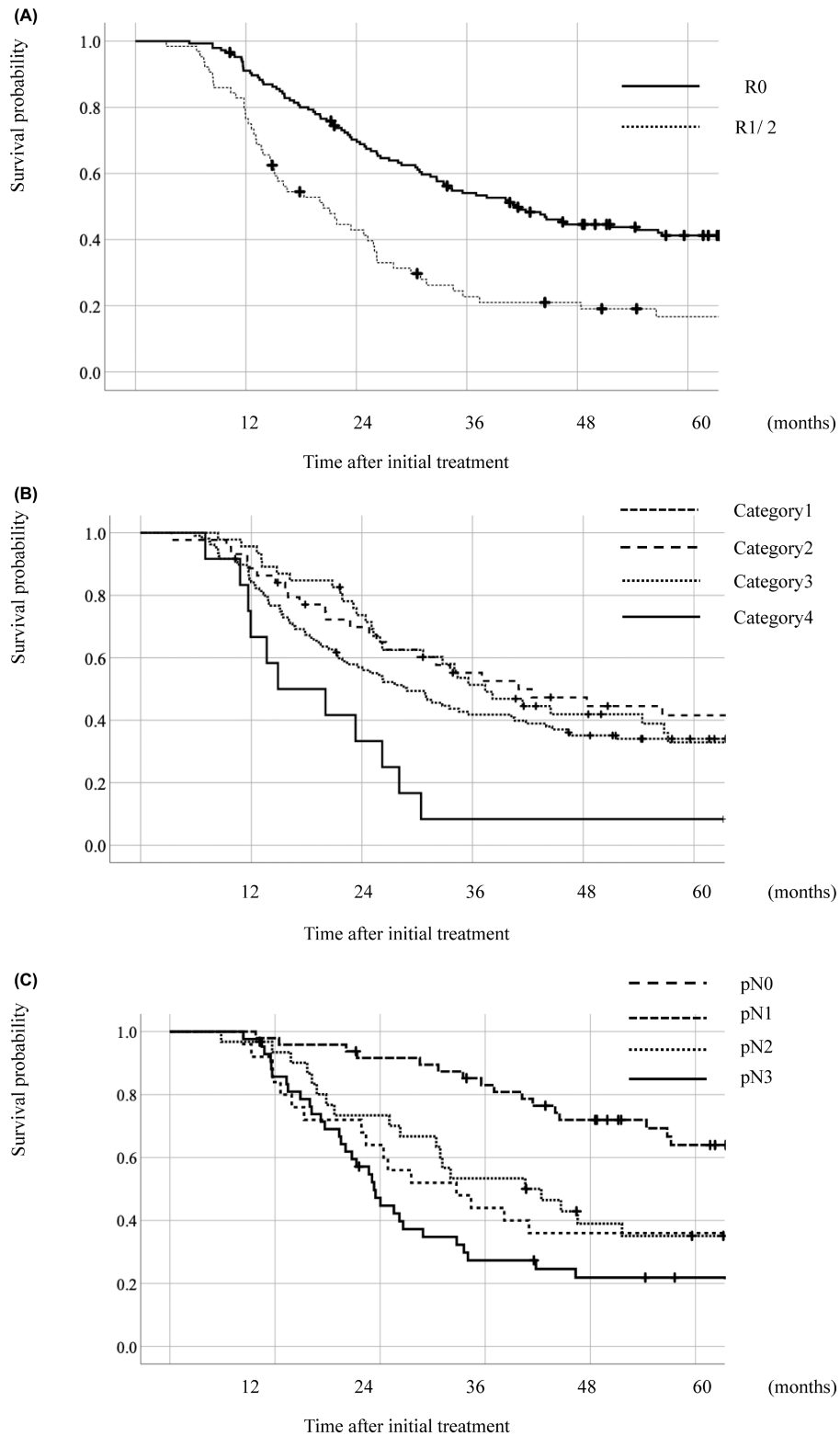
FIGURE 1 Overall survival curve according to the R status (A), Yoshida category (B), and pN (C).

literature and ongoing trials.[13] In non-randomized studies, an apparent survival benefit was observed for local treatment compared with systemic therapy alone for oligometastatic esophagogastric cancer.

Stage IV AGC has various metastatic forms, including extra-regional LNs, the liver, and the peritoneum. Heterogeneity makes it

difficult to categorize patients with stage IV AGC into a single group and treat them using the same strategy. Some prospective studies have focused on single non-curative factors. There were four studies on para-aortic LN metastasis,[14–17] two on peritoneal metastasis,[18,19] and only one on liver metastasis.[20] In contrast, most studies

TABLE 2 Univariate and multivariate analysis of OS in patients with R0 resection.

Variables	n	Univariate	Multivariate	
		p value	Hazard ratio	p value
Sex				
Male	106	0.175	1.315 (0.812–2.131)	0.265
Female	40			
Age				
≥65 years	80	0.416		
<65 years	66			
Histology				
Undifferentiated	79	0.150	1.431 (0.924–2.217)	0.108
Differentiated	69			
Hepatic metastasis				
Yes	30	0.577		
No	116			
Peritoneal metastasis				
Yes	61	0.791		
No	85			
Distant LN metastasis				
Yes	64	0.265		
No	82			
Number of non-curative factors				
≥2	12	0.056	1.527 (0.769–3.033	0.226
1	134			
Duration of chemotherapy				
≥90 days	61	0.552		
<90 days	85			
Induction chemotherapy				
First line	136	0.790		
Second line	10			
Procedure				
TG	84	0.084	1.409 (0.893–2.223)	0.141
PG/DG	62			
Metastasectomy				
Yes	62	0.778		
No	84			
Postoperative complication (CD grade > II)				
Yes	28	0.071	1.238 (0.725–2.115)	0.435
No	118			
pT				
pT4	42	<0.001	1.544 (0.956–2.493)	0.076
pT0–3	104			
pN				
pN+	98	<0.001	2.827 (1.559–5.126)	<0.001
pN0	48			

TABLE 2 (Continued)

Variables	n	Univariate p value	Multivariate Hazard ratio	p value
Pathological effect				
Gr0–2	132	0.013	2.178 (0.655–7.246)	0.204
Gr3	14			
Adjuvant chemotherapy				
No	27	0.823		
Yes	119			

Abbreviations: CD, Clavien–Dindo; DG, distal gastrectomy; LN, lymph node; OS, overall survival; PG, proximal gastrectomy; TG, total gastrectomy.

covering various metastatic forms were retrospective from a single institution. No report was limited to R0 resection cases of CS, and a prognostic analysis for R0 resected cases has never been studied. In addition, the survival analysis for each metastatic site in R0 resection cases with a single metastasis has yet to be elucidated.

A recent retrospective global cohort study covering 1206 patients with stage IV AGC who underwent CS after chemotherapy with curative intent reported that the MSTs of all patients and patients who achieved R0 resection were 36.7 months and 56.6 months.[10] It was concluded that surgery aimed at R0 resection after induction chemotherapy could now be considered an established treatment strategy for stage IV AGC. Our survival data appear to be equivalent; however, there are three differences. First, prognostic factors such as patient characteristics, metastasectomy, pathological effects, and adjuvant chemotherapy were not analyzed. Second, because their registered patients were treated between 2001 and 2014, regimens different from those used in our study may have been selected and some of them might not have received adjuvant chemotherapy. In contrast, all our patients were treated with adjuvant chemotherapy which was considered standard care. Third, the authors did not refer to initial metastasis and relapse patterns.

Several studies have been conducted to elucidate prognostic factors for CS in stage IV AGC. Various clinical factors, such as performance status, histological type, tumor size, and number of non-curative factors, and surgical factors, such as surgical curability (R0), pathological response, pN status, ypTNM, and postoperative chemotherapy, have been suggested as predictors of OS.[6–9,21–26] Most studies showed that R0 resection is an independent prognostic factor.[6,8,21,25,27] From the above result, it seems fairly evident that R0 resection will be an essential and strong prognostic factor for successful treatment. On this basis, we further analyzed the prognostic factors in patients who achieved R0 resection. Identifying two prognostic factors (pathological T4 and pathological N positivity) would be useful for predicting prognosis after R0 resection. The survival curve according to the pT and pN status indicated an extremely poor prognosis in both pT4 and pN positive groups (Figure 1C, Figure S1). Patients with longer chemotherapy who showed a treatment response likely experienced further shrinkage of the local tumor. However, the mean duration of preoperative chemotherapy did neither significantly differ between the pT1-3 and pT4 groups (155 days

vs. 142 days, $p = 0.32$) nor between the pN0 and pN positive groups (166 days vs. 144 days, $p = 0.20$).

The induction chemotherapy period and timing of surgery for CS also remain controversial points. A consensus by the European group states that local treatment for oligometastatic diseases after a median of 18 weeks (4.5 months) of systemic therapy is recommended.[13] The CONVO-GC-1 study revealed that the median duration of induction chemotherapy was 92 days (3.1 months) in category 1, 135.5 days (4.5 months) in category 2, 158 days (5.3 months) in category 3, and 174 days (5.8 months) in category 4.[10] It should logically follow that the larger the tumor load, the longer it takes to shrink. In our study, the median duration of induction chemotherapy was 3.2 months. This short duration could be attributed to the fact that 51% of our patients were classified into category 1, which was characterized by a smaller tumor load.

Despite multiple reports on CS, few have mentioned the patterns of relapse. Our curatively resected cohort with only a single non-curative factor resulted in 62% of relapse cases. Relapse patterns were divided into the peritoneum (51%), LNs (33%), and liver (17%). Patterns of relapse at the site of initial metastasis were seen in the peritoneum (89%), liver (58%), and LNs (62%), respectively. In CS, clinically invisible lesions are usually regarded as a complete response, and metastasectomy is omitted. However, our data indicate the difficulty in achieving a complete clinical response. It would be interesting to elucidate whether a longer duration of induction chemotherapy or the administration of adjuvant chemotherapy after CS can control occult unresectable disease and improve survival; however, there are no reports in this regard. Similarly, we found that both induction chemotherapy for >90 days and adjuvant chemotherapy were not prognostic factors. A recent prospective randomized controlled trial (RCT) for limited metastases (RENAISSANCE)[28] set only 8 weeks (four cycles of FLOT) as the duration for induction chemotherapy. Even when limited metastases are targeted, more effective regimens like FLOT would not necessarily require a longer duration for induction chemotherapy.

As shown in Figure 2, no significant difference exists in survival among the three types of initial metastatic sites in the 132 patients with a single non-curative factor. Surprisingly, survival after CS did not depend on the metastatic site as long as R0 resection could be achieved. A recent report based on the National

TABLE 3 Univariate and multivariate analysis of RFS in patients with R0 resection.

Variables	n	Univariate p value	Multivariate Hazard ratio	p value
Sex				
Male	106	0.476		
Female	40			
Age				
≥65 years	80	0.752		
<65 years	66			
Histology				
Undifferentiated	79	0.316		
Differentiated	69			
Hepatic metastasis				
Yes	30	0.109	1.319 (0.819–2.127)	0.255
No	116			
Peritoneal metastasis				
Yes	61	0.815		
No	85			
Distant LN metastasis				
Yes	64	0.989		
No	82			
Number of non-curative factors				
≥2	12	0.045	1.550 (0.786–3.056)	0.206
1	134			
Duration of chemotherapy				
≥90 days	61	0.591		
<90 days	85			
Induction chemotherapy				
First line	136	0.769		
Second line	10			
Procedure				
TG	84	0.340		
PG/DG	62			
Metastasectomy				
Yes	62	0.256		
No	84			
Postoperative complication (CD grade > II)				
Yes	28	0.104	1.324 (0.804–2.180)	0.270
No	118			
pT				
pT4	42	<0.001	1.977 (1.288–3.035)	0.002
pT0–3	104			
pN				
pN+	98	<0.001	2.131 (1.251–3.632)	0.005
pN0	48			

TABLE 3 (Continued)

		Univariate	Multivariate	
Variables	**n**	**_p_ value**	**Hazard ratio**	**_p_ value**
Pathological effect				
Gr0–2	132	0.004	4.132 (0.971–17.543)	0.055
Gr3	14			
Adjuvant chemotherapy				
No	27	0.296		
Yes	119			

Abbreviations: CD, Clavien–Dindo; DG, distal gastrectomy; LN, lymph node; PG, proximal gastrectomy; RFS, recurrence-free survival; TG, total gastrectomy.

TABLE 4 Background of patients with a single non-curative factor.

	Peritoneum _n_ = 54 (%)	Liver _n_ = 25 (%)	Lymph node _n_ = 53 (%)
Sex			
Male/female	35 (65)/19 (35)	24 (96)/1 (4)	38 (72)/15 (28)
Histology			
Differentiated/ undifferentiated	13 (24)/41 (76)	18 (72)/7 (28)	27 (51)/26 (49)
Intraperitoneal chemotherapy			
Presence/absence	18 (33)/36 (67)	0/25 (100)	0/53 (100)
Postoperative complication (CD grade > II)			
Yes/no	11 (20)/43 (80)	4 (16)/21 (84)	11 (21)/42 (79)
pT			
pT0–3/pT4	34 (63)/20 (37)	16 (64)/9 (36)	44 (83)/9 (17)
pN			
pN0/pN+	22 (41)/32 (59)	7 (28)/18 (72)	18 (34)/35 (66)
Pathological effect			
Gr0–2/G3	48 (89)/5 (11)	24 (96)/1 (4)	47 (89)/6 (11)
Adjuvant chemotherapy			
Yes/no	50 (93)/4 (7)	21 (84)/4 (16)	38 (72)/15 (28)

Note: Data are presented as _n_ (%).
Abbreviation: CD, Clavien–Dindo.

Cancer Database demonstrated that clinical stage IV AGC with distant LNs has a better prognosis than other stage IV AGCs.[29] Peritoneal metastasis is generally considered to have the worst prognosis among all metastases in stage IV AGC. This discrepancy is probably because the peritoneal metastasis group included more patients who received adjuvant chemotherapy than the other groups, as shown in Table 4. The peritoneal metastasis group also included 18 (33%) patients receiving intraperitoneal chemotherapy (Table 4). No significant difference in background data (including the rates of P0CY1, pT, pN, and pathological responses) and survival data were found between the intraperitoneal chemotherapy group and the only intravenous chemotherapy group (MST: 34.5 months vs. 45.1 months; _p_ = 0.196, log-rank test). This suggests that intraperitoneal chemotherapy is not the main cause for the observed discrepancy in survival.

As initial metastasis sites, the LNs and liver do not always cause peritoneal metastases, as shown in Figure 3. Because it is naturally difficult to administer intensive chemotherapy after gastrectomy, it is desirable to strengthen preoperative treatment. Most adjuvant chemotherapy regimens in our study used S1 monotherapy. Recently, neoadjuvant chemotherapy regimens with high response rates, such as DOS and FLOT, have been developed and are expected to improve AGC long-term outcomes.[30,31] Further studies on adjuvant chemotherapy after CS are required.

Recent revolutionary progress in immune checkpoint inhibitors (ICIs) has paved the way for a new era of cancer immunotherapy, leading to a paradigm shift in cancer treatment.[32] In particular, inhibition of the programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) axis with ICIs, including nivolumab and pembrolizumab, has been introduced as a novel treatment strategy for
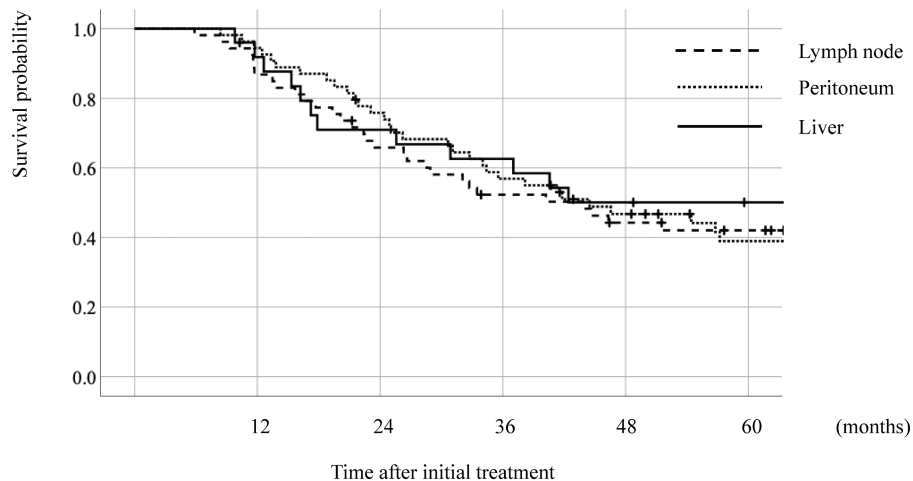
FIGURE 2 Overall survival curve of 132 patients with a single non-curative factor according to the initial metastatic site.
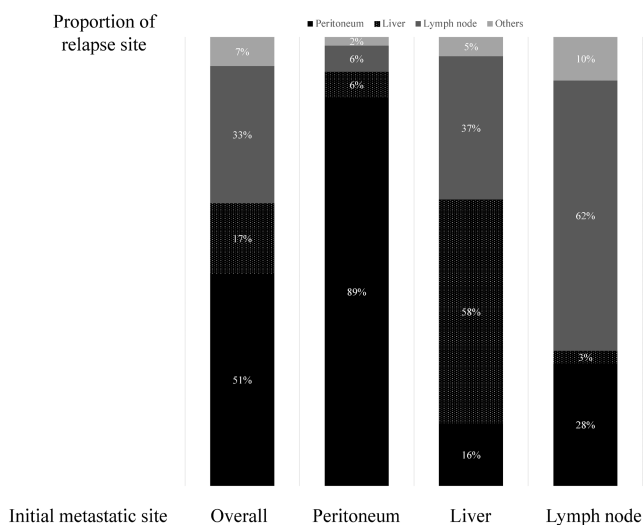

FIGURE 3 Association between initial metastatic site and relapse site in 132 patients with a single non-curative factor.

AGC. Although monotherapy with these drugs can induce marked and durable responses in approximately 10% of patients,[33] two recent RCTs have demonstrated that first-line combination treatment with chemotherapy is a new standard treatment for AGC.[34,35] Both trials found that ICI plus chemotherapy significantly improves survival and objective response rates. Although we did not use chemotherapy with ICI in our study population, it may lead to an increase in the CS rate and an improvement in OS for patients with stage IV AGC.

A limitation of our study is its retrospective and nonrandomized design. Additionally, this study did not include a control group. Patients who responded to systemic therapy were offered subsequent local treatment, and these responders had improved OS irrespective of local treatment. In this respect, our results must be considered before they can be generalized in clinical practice. We included all stage IV AGCs, but some stage IV tumors, such as

only #16a2/b1 LN metastasis, cytology positive, and single liver metastasis, could be considered marginally resectable lesions. Hence, it is important to strictly define the term "conversion surgery" and establish a common understanding of unified treatment strategies. RCTs should be conducted to demonstrate the survival benefits of CS. The Renaissance trial by Al-Batran et al. addressed the benefits of surgical resection of the primary tumor and metastases plus systemic therapy over systemic therapy alone in patients with gastric or gastroesophageal junction cancer with synchronous OMC.[28]

5 | CONCLUSIONS

CS for patients with stage IV AGC and R0 resection can lead to longer survival. Patients with pathological T4 and pathological N positivity were eligible for intensive adjuvant therapy after CS. Survival after CS did not depend on the metastatic site because R0 resection could be obtained.

AUTHOR CONTRIBUTIONS

All authors contributed to the study's conception and design. Atsushi Takeno and Masaaki Motoori performed material preparation, data sample collection, and analysis. Atsushi Takeno wrote the first draft of the manuscript, and all authors commented on previous versions. All the authors have read and approved the final version of the manuscript.

CONFLICT OF INTEREST STATEMENT

ETHICS STATEMENTS

Approval of the research protocol: This study was approved by the local ethics committees of each participating institution and was in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1964 and later versions.

Informed Consent: N/A.

Registry and the Registration No. of the study: N/A.

Animal Studies: N/A.

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REFERENCES

1. Ohtsu A, Shimada Y, Shirao K, Boku N, Hyodo I, Saito H, et al. Randomized phase III trial of fluorouracil alone versus fluorouracil plus cisplatin versus uracil and tegafur plus mitomycin in patients with unresectable, advanced gastric cancer: the Japan Clinical Oncology Group Study (JCOG9205). J Clin Oncol. 2003;21(1):54–9.
2. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastrooesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet. 2010;376(9742):687–97.
3. Fujitani K, Yang HK, Mizusawa J, Kim YW, Terashima M, Han SU, et al. Gastrectomy plus chemotherapy versus chemotherapy alone for advanced gastric cancer with a single non-curable factor (REGATTA): a phase 3, randomised controlled trial. Lancet Oncol. 2016;17(3):309–18.
4. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2018 (5th edition). Gastric Cancer. 2021;24(1):1–21.
5. Yoshida K, Yamaguchi K, Okumura N, Tanahashi T, Kodera Y. Is conversion therapy possible in stage IV gastric cancer: the proposal of new biological categories of classification. Gastric Cancer. 2016;19(2):329–38.
6. Fukuchi M, Ishiguro T, Ogata K, Suzuki O, Kumagai Y, Ishibashi K, et al. Prognostic role of conversion surgery for unresectable gastric cancer. Ann Surg Oncol. 2015;22(11):3618–24.
7. Solaini L, Ministrini S, Bencivenga M, D'Ignazio A, Marino E, Cipollari C, et al. Conversion gastrectomy for stage IV unresectable gastric cancer: a GIRCG retrospective cohort study. Gastric Cancer. 2019;22(6):1285–93.
8. Sato S, Kunisaki C, Tanaka Y, Sato K, Miyamoto H, Yukawa N, et al. Curative-intent surgery for stage IV advanced gastric cancer: who can undergo surgery and what are the prognostic factors for long-term survival? Ann Surg Oncol. 2019;26(13):4452–63.
9. Chen GM, Yuan SQ, Nie RC, Luo TQ, Jiang KM, Liang CC, et al. Surgical outcome and long-term survival of conversion surgery for advanced gastric cancer. Ann Surg Oncol. 2020;27(11):4250–60.
10. Yoshida K, Yasufuku I, Terashima M, Young Rha S, Moon Bae J, Li G, et al. International retrospective cohort study of conversion therapy for stage IV gastric cancer 1 (CONVO-GC-1). Ann Gastroenterol Surg. 2022;6(2):227–40.
11. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg. 2009;250(2):187–96.
12. Hellman S, Weichselbaum RR. Oligometastases. J Clin Oncol. 1995;13(1):8–10.
13. Kroese TE, van Hillegersberg R, Schoppmann S, Deseyne PRAJ, Nafteux P, Obermannova R, et al. Definitions and treatment of oligometastatic oesophagogastric cancer according to multidisciplinary tumour boards in Europe. Eur J Cancer. 2022;164:18–29.
14. Yoshikawa T, Sasako M, Yamamoto S, Sano T, Imamura H, Fujitani K, et al. Phase II study of neoadjuvant chemotherapy and extended surgery for locally advanced gastric cancer. Br J Surg. 2009;96(9):1015–22.
15. Tsuburaya A, Mizusawa J, Tanaka Y, Fukushima N, Nashimoto A, Sasako M, et al. Neoadjuvant chemotherapy with S-1 and cisplatin followed by D2 gastrectomy with para-aortic lymph node dissection for gastric cancer with extensive lymph node metastasis. Br J Surg. 2014;101(6):653–60.
16. Ito S, Sano T, Mizusawa J, Takahari D, Katayama H, Katai H, et al. A phase II study of preoperative chemotherapy with docetaxel, cisplatin, and S-1 followed by gastrectomy with D2 plus para-aortic lymph node dissection for gastric cancer with extensive lymph node metastasis: JCOG1002. Gastric Cancer. 2017;20(2):322–31.
17. Wang Y, Yu YY, Li W, Feng Y, Hou J, Ji Y, et al. A phase II trial of Xeloda and oxaliplatin (XELOX) neo-adjuvant chemotherapy followed by surgery for advanced gastric cancer patients with para-aortic lymph node metastasis. Cancer Chemother Pharmacol. 2014;73(6):1155–61.
18. Ishigami H, Kitayama J, Kaisaki S, Hidemura A, Kato M, Otani K, et al. Phase II study of weekly intravenous and intraperitoneal paclitaxel combined with S-1 for advanced gastric cancer with peritoneal metastasis. Ann Oncol. 2010;21(1):67–70.
19. Ishigami H, Fujiwara Y, Fukushima R, Nashimoto A, Yabusaki H, Imano M, et al. Phase III trial comparing intraperitoneal and intravenous paclitaxel plus S-1 versus cisplatin plus S-1 in patients with gastric cancer with peritoneal metastasis: PHOENIX-GC trial. J Clin Oncol. 2018;36(19):1922–9.
20. Fujitani K, Kurokawa Y, Takeno A, Kawabata R, Omori T, Imamura H, et al. Prospective multicenter interventional study of surgical resection for liver metastasis from gastric cancer: R0 resection rate, and operative morbidity and mortality. Ann Surg Oncol. 2022;29(2):924–32.
21. Satoh S, Okabe H, Teramukai S, Hasegawa S, Ozaki N, Ueda S, et al. Phase II trial of combined treatment consisting of preoperative S-1 plus cisplatin followed by gastrectomy and postoperative S-1 for stage IV gastric cancer. Gastric Cancer. 2012;15(1):61–9.
22. Kanda T, Yajima K, Kosugi S, Ishikawa T, Ajioka Y, Hatakeyama K. Gastrectomy as a secondary surgery for stage IV gastric cancer patients who underwent S-1-based chemotherapy: a multi-institute retrospective study. Gastric Cancer. 2012;15(3):235–44.
23. Sato Y, Ohnuma H, Nobuoka T, Hirakawa M, Sagawa T, Fujikawa K, et al. Conversion therapy for inoperable advanced gastric cancer patients by docetaxel, cisplatin, and S-1 (DCS) chemotherapy: a multi-institutional retrospective study. Gastric Cancer. 2017;20(3):517–26.
24. Mieno H, Yamashita K, Hosoda K, Moriya H, Higuchi K, Azuma M, et al. Conversion surgery after combination chemotherapy of docetaxel, cisplatin and S-1 (DCS) for far-advanced gastric cancer. Surg Today. 2017;47(10):1249–58.

25. Beom SH, Choi YY, Baek SE, Li SX, Lim JS, Son T, et al. Multidisciplinary treatment for patients with stage IV gastric cancer: the role of conversion surgery following chemotherapy. BMC Cancer. 2018;18(1):1116.

26. Jeong GS, Lee IS, Park YS, Kim BS, Yoo MW, Yook JH, et al. Advantages of ypTNM staging in post-surgical prognosis for initially unresectable or stage IV gastric cancers. J Gastric Cancer. 2020;20(3):233–44.

27. Kano Y, Ichikawa H, Hanyu T, Muneoka Y, Ishikawa T, Aizawa M, et al. Conversion surgery for stage IV gastric cancer: a multicenter retrospective study. BMC Surg. 2022;22(1):428.

28. Al-Batran SE, Goetze TO, Mueller DW, Vogel A, Winkler M, Lorenzen S, et al. The Renaissance (AIO-FLOT5) trial: effect of chemotherapy alone vs. chemotherapy followed by surgical resection on survival and quality of life in patients with limited-metastatic adenocarcinoma of the stomach or esophagogastric junction – a phase III trial of the German AIO/CAO-V/CAOGI. BMC Cancer. 2017;17(1):893.

29. Zhan PL, Canavan ME, Ermer T, Pichert MD, Li AX, Maduka RC, et al. Association between metastatic pattern and prognosis in stage IV gastric cancer: potential for stage classification reform. Ann Surg Oncol. 2023;30(7):4180–91.

30. Kurokawa Y, Kawase T, Takeno A, Furukawa H, Yoshioka R, Saito T, et al. Phase 2 trial of neoadjuvant docetaxel, oxaliplatin, and S-1 for clinical stage III gastric or esophagogastric junction adenocarcinoma. Ann Gastroenterol Surg. 2023;7(2):247–54.

31. Al-Batran SE, Homann N, Pauligk C, Goetze TO, Meiler J, Kasper S, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. Lancet. 2019;393(10184):1948–57.

32. Sharma P, Allison JP. The future of immune checkpoint therapy. Science. 2015;348(6230):56–61.

33. Kang YK, Boku N, Satoh T, Ryu MH, Chao Y, Kato K, et al. Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017;390(10111):2461–71.

34. Shitara K, Ajani JA, Moehler M, Garrido M, Gallardo C, Shen L, et al. Nivolumab plus chemotherapy or ipilimumab in gastro-oesophageal cancer. Nature. 2022;603(7903):942–8.

35. Kang YK, Chen LT, Ryu MH, Oh DY, Oh SC, Chung HC, et al. Nivolumab plus chemotherapy versus placebo plus chemotherapy in patients with HER2-negative, untreated, unresectable advanced or recurrent gastric or gastro-oesophageal junction cancer (ATTRACTION-4): a randomised, multicentre, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2022;23(2):234–47.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.