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Curative-Intent Surgery for Stage IV Advanced Gastric Cancer: Who Can Undergo Surgery and What Are the Prognostic Factors for Long-Term Survival?

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ABSTRACT

Background. A retrospective study was performed to evaluate the predictive factors for performing curative-intent surgery and prognostic factors for long-term survival of patients undergoing surgery for stage IV gastric cancer.

Patients and Methods. Between 2001 and 2017, 271 patients with stage IV gastric cancer with distant metastasis who underwent systemic chemotherapy were enrolled. Logistic regression analysis was performed to evaluate predictive factors for curative-intent surgery. Cox proportional hazards regression model was applied for patients who were subsequently treated with curative-intent surgery to identify prognostic factors for long-term survival.

Results. Curative-intent surgery was performed in 48 patients (17.7%). Median survival time was significantly longer in the surgery group than in the nonsurgery group (53 vs. 11 months, $p < 0.0001$). R0 resection was performed in 35 patients (72.9%). The three-year overall survival (OS) rates of the R0, R1, and R2 surgery groups were 75.4%, 33.3%, and 25.0%, respectively ($p = 0.0002$). Logistic regression analysis revealed that lymphogenous distant metastasis alone (odds ratio = 3.276, $p = 0.004$), positive lavage cytology alone (6.394, 0.014), doublet or triplet chemotherapy (4.064, 0.034), and high Glasgow

prognostic score (0.276, 0.001) were independent predictive factors for performing curative-intent surgery. Among patients undergoing surgery, the Cox proportional hazards regression model for OS showed that R0 surgery was an independent prognostic factor for favorable OS (hazard ratio 0.188, $p = 0.022$).

Conclusions. Patients with lymphogenous distant metastasis alone, P0CY1 alone, good immunonutritional status, and doublet/triplet chemotherapy are candidates for performing effective curative-intent surgery. R0 surgery is crucial for improving long-term survival after surgery.

Globally, gastric cancer (GC) is the fourth leading cause of death from cancer in both sexes (782,685 deaths, 8.2% of total).[1] Together with advancements in chemotherapy, several randomized controlled studies have reported improved patient survival; however, the median survival time (MST) is limited to 11–18 months[2–5] in stage IV GC. A randomized controlled trial comparing gastrectomy followed by chemotherapy with chemotherapy alone in advanced GC with single noncurative factor did not show superiority of the gastrectomy group with respect to overall survival (OS).[6] Therefore, chemotherapy remains the main therapeutic approach for stage IV GC,[7] and as stated in the Japanese treatment guidelines, surgery for this cohort is usually confined to palliative resection or bypass operation to relieve symptoms.[8–10]

Curative-intent surgery is surgical resection after downstaging or disease control by chemotherapy for patients with initially unresectable gastric cancer. This type

of surgery is often referred to as conversion surgery, which is sometimes difficult to distinguish clearly from curative surgery scheduled after neoadjuvant chemotherapy.[11] Recently, several retrospective studies showed favorable outcomes of curative-intent surgery in cases responding to systemic chemotherapy with and without intraperitoneal chemotherapy.[12–19] In these studies, the MSTs of patients who successfully underwent surgery were 19–56 months, representing favorable long-term survival rates compared with those receiving chemotherapy alone. Although curative-intent surgery for stage IV advanced GC cases may be one of the main roles performed by a surgical oncologist,[20] predictive factors for performing curative-intent surgery and prognostic factors for OS remain unclear.

In the present study, we retrospectively evaluated therapeutic outcomes in stage IV GC patients to clarify the indication for curative-intent surgery and the significance after surgery.

PATIENTS AND METHODS

Human Rights Statement and Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and in compliance with the Helsinki Declaration of 1964 and later versions. We disclosed all information to the patients. Participating patients were excluded only when they specified that they were unwilling to participate.

Patients

From January 2000 to December 2017, a series of 271 patients diagnosed as having stage IV gastric cancer underwent chemotherapy at the Department of Surgery, Gastroenterological Center, Yokohama City University. Tumor staging and histopathological grading were performed according to the 3rd edition of the Japanese Classification of Gastric Carcinoma.[21] Patients who had only locally advanced lesion, such as pancreatic invasion which was categorized as stage IV in the previous Japanese Classification of Gastric Carcinoma,[22] were excluded from this study. After sufficient discussion in the preoperative conference, 48 patients underwent surgery with curative intent.

In all patients, tumors were histologically confirmed as adenocarcinoma and diagnosed as stage IV via various techniques of imaging, with and without staging laparoscopy. Computed tomography (CT), upper gastroenterological endoscopy, and upper gastroenterological series were performed for pretherapeutic

evaluation. [18F]-Fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET)/CT was performed in some cases if distant metastasis was suspected. Some patients underwent staging laparoscopy to evaluate whether there was peritoneal dissemination (P1) and/or positive lavage cytology (CY1). Distant metastatic types were classified into five categories: hematogenous metastasis alone, lymphogenous distant metastasis alone, peritoneal dissemination alone with and without positive lavage cytology, positive lavage cytology alone, and multiple noncurative factors. According to the new biological classification for stage IV GC proposed by Yoshida et al. (Yoshida's classification),[20] patients with CY1 or some paraaortic lymph node metastasis or solitary liver metastasis below 5 cm were defined as the potentially resectable group (category 1). The authors describe that category 1 should usually be excluded from the concept of conversion surgery, because resection of such patients is technically straightforward. However, there is no evidence of favorable long-term results in this population. In the real world, patients in category 1 undergo systemic chemotherapy before surgery, thus we included this population in the current study and defined every surgery for stage IV advanced gastric cancer patients after initial chemotherapy as "curative-intent surgery."

This retrospective study protocol conformed to the provisions of the Declaration of Helsinki and was approved by the Institutional Review Board for the Use of Human Subjects at the Yokohama City University School of Medicine (approval no. 2019-012). According to the law of personal information protection, we published the survey items of this study for patients to give them a chance to opt out of this study (URL: https://www.yokohama-cu.ac.jp/amedrc/ethics/ethical/center_optout.html).

Chemotherapy

The chemotherapy regimens were as follows: S-1 monotherapy,[23] S-1 plus cisplatin,[3] S-1 plus docetaxel,[24–26] S-1 plus oxaliplatin,[5] S-1 plus docetaxel plus cisplatin,[27] capecitabine plus cisplatin,[28] capecitabine plus cisplatin plus trastuzumab,[2] and others. All regimens followed the Japanese gastric cancer guidelines[7] or regimens of clinical trials in which the patients were enrolled after informed consent was obtained.

Assessment of Efficacy of Chemotherapy

CT, upper gastroenterological endoscopy, and upper gastroenterological series were performed after two or three cycles of administration to evaluate clinical response of the target lesions, and the stage was rediagnosed. Tumors (1) without pancreatic head invasion, (2) with

some resectable paraaortic lymph node metastasis (located between 16b1 and 16a2),[21] (3) with solitary liver metastasis, (4) with disappearance of or a few resectable peritoneal disseminated nodules, and (5) with disappearance of other distant organ metastasis were regarded as curatively resectable and considered as being favorable for curative-intent surgery. After sufficient discussion in the multidisciplinary preoperative conference, 48 patients (17.7%) finally underwent surgery with curative intent.

Surgery

After staging laparoscopy, standard D2 gastrectomy or more extended lymph node dissection with and without metastasectomy was performed via laparotomy with curative intent. Even if lavage cytology was positive (CY1), gastrectomy was performed if there were no other noncurable factors. Distal gastrectomy was performed for tumors located in the middle and lower third of the stomach when the proximal margin was confirmed to be microscopically negative by intraoperative rapid pathological examination. By contrast, total gastrectomy was selected for tumors in the upper third of the stomach or those spreading in the entire of the stomach.

Postoperative complications were assessed in all patients receiving gastrectomy. Postoperative morbidity was listed according to Clavien–Dindo classification of surgical complications.[29] R0, R1, and R2 resection was defined as microscopically curative resection, microscopic residual tumor, and macroscopic residual tumor, respectively. Pathological response of the primary tumor after preoperative chemotherapy was assessed according to the classification defined by the Japanese Gastric Cancer Association (JGCA).[21] Based on the surgical specimen of the primary lesion, tumor regression was graded and divided into five categories as follows: grade 0, no evidence of effect; grade 1a, < 1/3 affected; grade 1b, $\geq$ 1/3 and < 2/3 affected; grade 2 $\geq$ 2/3 affected; and grade 3, no viable tumor cells remaining. Postoperative chemotherapy was performed if a patient maintained good performance status (PS) and nutritional status, after obtaining informed consent.

Statistical Analysis

Continuous variables are expressed as median (interquartile range, IQR). Data of the different groups were compared by Wilcoxon test. Categorical data were analyzed by Chi square test. We measured OS from date of first administration of chemotherapy to date of last follow-up. We measured disease-free survival (DFS) from date of curative-intent surgery to date of detection of recurrence or

death from any causes excluding R2 surgery cases. OS rates after start of treatment were calculated according to the Kaplan–Meier method, and differences between groups were tested for significance using the log-rank test. In univariate analysis of predicting curative-intent surgery, each distant metastatic type was analyzed using the multiple noncurative metastases type as a reference. Multivariate analysis for predicting curative-intent surgery by logistic regression analysis included covariates that gave values of $P < 0.1$ on univariate analysis. Multivariate survival analysis by a Cox proportional hazards regression model included covariates that gave values of $P < 0.1$ on univariate survival analysis. All statistical analyses were performed using JMP® 13 (SAS Institute Inc., Cary, NC, USA). Differences with probability values $P < 0.05$ were considered as significant.

RESULTS

Selection of Patients for Curative-Intent Surgery

During the period of chemotherapy for 271 stage IV GC patients, 202 patients showed progressive disease, 4 patients changed hospital, 2 patients died from other disease, and 15 patients who showed macroscopic peritoneal dissemination by exploratory laparotomy could not undergo surgery. Finally, 48 patients underwent surgery with curative intent (Fig. 1).

Patient Characteristics of Registered Patients

Table 1 summarizes the demographics and tumor characteristics of the 271 patients who underwent systemic chemotherapy. There were 198 (73.1%) men. Median age
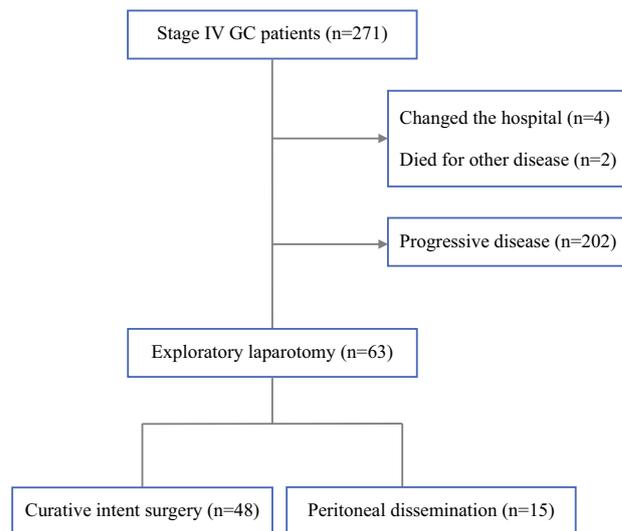

FIG. 1 Patient flow diagram

TABLE 1 Characteristics of stage IV gastric cancer patients

Variable	$n = 271$ (%)
Sex (M/F)	198 (73.1)/73 (26.9)
Age (years)	68 (61–73)[a]
Location of the tumor (U/M/L)	101 (37.3)/83 (30.6)/87 (32.1)
Comorbidities	
Cardiovascular	17 (6.3)
Pulmonary	11 (4.1)
Diabetes mellitus	21 (7.8)
Macroscopic type (0/1/2/3/4)	3 (1.1)/5 (1.8)/67 (24.7)/141 (52.0)/55 (20.3)
Histological differentiation (G1/G2/G3)[b]	51(18.8)/71 (26.2)/149 (55.0)
Tumor diameter (cm)	8.0 (6.0–11.0)[a]
Distant metastatic site	
Hematogenous metastasis	46 (17.0)
Lymphogenous metastasis	60 (22.1)
Peritoneal dissemination[c]	87 (32.1)
Positive lavage cytology[d]	10 (3.7)
Multiple noncurable factors	68 (25.1)
Ex-lap (none/open/laparoscopy)	158 (58.3)/24 (8.9)/89 (32.8)
Chemotherapy regimen	
S-1	37 (13.6)
S-1 + cisplatin	48 (17.7)
S-1 + docetaxel	90 (33.2)
S-1 + oxaliplatin	34 (12.5)
S-1 + docetaxel + cisplatin	9 (3.3)
Capecitabine + cisplatin	26 (9.6)
Capecitabine + cisplatin + trastuzumab	10 (3.7)
Other regimens	17 (6.3)

Ex-lap exploratory laparotomy

[a]Median (IQR)

[b]According to TNM classification, G1 represents well-differentiated adenocarcinoma, G2 represents moderately differentiated adenocarcinoma, and G3 represents poorly differentiated adenocarcinoma and others

[c]With or without positive lavage cytology

[d]Excluding macroscopic peritoneal dissemination

was 68 (IQR, 61–73) years. The most frequent comorbidity was diabetes mellitus (7.8%). Most frequently, the tumor site was the upper third (U) ($n = 101$, 37.3%) and the macroscopic type was type 3 ($n = 141$, 52.0%). A total of 149 patients (55.0%) had poorly differentiated or other type of histological differentiation, and median tumor diameter was 8.0 cm (IQR 6.0–11.0 cm). A total of 113 patients (32.8%) underwent exploratory laparotomy prior to initial chemotherapy, being open laparotomy for 24 patients and staging laparoscopy for 89 patients. With respect to distant metastatic site, peritoneal dissemination alone was highly observed (32.1%). Of these, 218 patients (80.4%) received S-1-based regimen and 36 patients (13.3%) received capecitabine-based regimen.

Patient Characteristics of Patients Who Underwent Curative-Intent Surgery for Stage IV Advanced GC

Table 2 summarizes the demographics and tumor characteristics of the patients who underwent curative-intent surgery. There were 30 (62.5%) men. Median age was 67 years (IQR 59–73 years). The tumor was frequently detected in the upper third (U) ($n = 20$, 41.7%), and type 3 tumor was macroscopically frequent ($n = 27$, 56.3%). Regarding distant metastatic type, lymphogenous distant metastasis alone ($n = 16$, 33.3%) and peritoneal dissemination alone ($n = 16$, 33.3%) were frequent. Among lymphogenous distant metastasis alone cases, there were 13 cases (81.3%) with paraaortic lymph node metastasis alone, 1 case with combination of paraaortic lymph node

TABLE 2 Characteristics, chemotherapy, and pathological details of patients who underwent curative-intent surgery for stage IV advanced gastric cancer

Variable	$n = 48$ (%)
Sex (M/F)	30 (62.5)/18 (37.5)
Age (years)	67 (59–73)[a]
Comorbidities	
Cardiovascular	5 (10.4)
Pulmonary	3 (6.3)
Diabetes mellitus	7 (14.6)
PNI	48.9 (43.1–52)[a]
BMI (kg/m^2)	22.4 (19.3–24.4)[a]
GPS (0/1/2)	35 (76.1)/8 (17.3)/2 (3)
Location of tumor (U/M/L)	20 (41.7)/16 (33.3)/12 (25.0)
Macroscopic type (0/1/2/3/4)	2 (4.2)/0 (0)/9 (18.8)/27 (56.3)/10 (20.8)
Histological differentiation (G1/G2/G3)[b]	10 (20.8)/14 (29.2)/24 (50.0)
Tumor diameter (cm)	9.4 (5.9–13.0)[a]
Metastatic site	
Hematogenous	3 (6.3)
Lymphogenous	16 (33.3)
Peritoneal dissemination[c]	16 (33.3)
Positive lavage cytology[d]	5 (10.4)
Multiple noncurable factors	8 (16.7)
Staging laparoscopy before chemotherapy (yes/no)	26 (54.2)/22 (45.8)
Chemotherapy	
S-1	2 (4.2)
S-1 + cisplatin	9 (18.8)
S-1 + docetaxel	12 (25.0)
S-1 + oxaliplatin	6 (12.5)
S-1 + docetaxel + cisplatin	5 (10.4)
Capecitabine + cisplatin	6 (12.5)
Capecitabine + cisplatin + trastuzumab	3 (6.3)
Other regimens	5 (10.4)
Duration of chemotherapy (months)	2.5 (1.7–5.2)[a]
Adjuvant chemotherapy (yes/no)	28 (63.6)/16 (36.3)
Type of resection (TG/DG)	40 (83.3)/8 (16.7)
Paraaortic lymph node dissection	16 (33.3)
Liver resection	2 (4.2)
Postoperative stay (days)	16 (12–34)[a]
Postoperative morbidity (grade 1/2/3a/3b)	2 (4.2)/6 (12.5)/6 (12.5)/2 (4.2)
Postoperative mortality	0 (0)
ypDepth (1/2/3/4)	6 (12.5)/2 (4.2)/13 (27.1)/27 (56.3)
ypN (0/1/2/3)	11 (23.4)/10 (21.3)/8 (17.0)/19 (39.6)
ypStage (I/II/III/IV)	6 (12.5)/7 (14.6)/19 (39.6)/16 (33.3)
Residual cancer (R0/R1/R2)	35 (72.9)/9 (18.8)/4 (8.3)
Pathological response (0/1a/1b/2/3)	4 (8.3)/30 (62.5)/8 (16.7)/6 (12.5)/0 (0)

PNI prognostic nutritional index, *BMI* body mass index, *GPS* Glasgow prognostic score, *TG* total gastrectomy, *DG* distal gastrectomy

[a]Median (IQR)

[b]According to TNM classification, G1 represents well-differentiated adenocarcinoma, G2 represents moderately differentiated adenocarcinoma, and G3 represents poorly differentiated adenocarcinoma and others

[c]With or without positive lavage cytology

[d]Excluding macroscopic peritoneal dissemination

and supraclavicular lymph node metastasis, 1 case with supraclavicular lymph node metastasis, and 1 case with other distant lymph node metastasis. The number of harvested paraaortic lymph nodes ranged from 0 to 20, and of pathologically positive paraaortic lymph nodes from 0 to 5. Among patients who underwent paraaortic lymph node dissection, the ≤ 3 positive para-aortic lymph node group showed better 5-year OS (%) than the other group (75.2 vs. 0, $P = 0.0001$).

Chemotherapy in Stage IV Patients Undergoing Conversion Surgery

Twenty-six patients (54.2%) underwent staging laparoscopy prior to initial chemotherapy (Table 2).

Principally, the chemotherapeutic regimens were selected according to the Japanese Gastric Cancer Treatment Guidelines.[30] However, other chemotherapeutic regimens were administered to some patients registered in clinical trials. Every patient underwent fluoropyrimidine-based regimens. The median duration of chemotherapy was 2.5 (1.7–5.2) months. Adjuvant chemotherapy was performed in 28 patients (63.6%) excluding the R2 surgery group. Regimens of postoperative chemotherapy for the R1 and R2 surgery group were as follows: S-1 monotherapy for four patients, S-1 plus oxaliplatin for two patients, S-1 plus docetaxel for one patient, docetaxel plus cisplatin for two patients, capecitabine plus cisplatin plus trastuzumab for one patient, irinotecan plus cisplatin for one patient, and nab-paclitaxel for one patient. One patient in the R2 surgery group could not receive postoperative chemotherapy due to poor performance status after gastrectomy.

Curative-Intent Surgery

Forty patients (83.3%) underwent total gastrectomy, and 8 patients (16.7%) patients underwent distal gastrectomy. Paraaortic lymph node dissection was performed in 16 patients (33.3%) who were diagnosed as having para-aortic lymph node metastasis before chemotherapy. Of the four patients with liver metastasis, two patients (4.2%) underwent partial liver resection and two patients showed complete remission with liver metastasis. A total of 14 patients (29.2%) suffered from Clavien–Dindo grade II or higher postoperative morbidity, although no postoperative mortality was observed (Table 2). Clavien–Dindo grade III postoperative morbidity occurred as follows: four cases (8.3%) of anastomotic leakage, two cases (4.2%) of duodenal stump leakage, two cases (4.2%) of pancreatic fistula, and one case (2.1%) of pleural effusion (with some overlap).

Pathological Details

Table 2 presents the yp depth, ypN, and ypStage results, revealing that yp T3/T4 was observed in 40 patients (83.3%), ypN(+) was seen in 37 patients (77.1%), and ypStage IV was observed in 16 patients (33.3%). R0 resection was performed in 35 patients (72.9%), R1 resection was performed in 9 patients (18.8%) (positive peritoneal cytology in 8 and positive margin in 1 case), and R2 resection was performed in 4 patients (8.3%) (peritoneal metastasis in 3 and unresectable paraaortic lymph node metastasis in 1 case). The pathological response rate of the primary tumors, including grade 1b, grade 2, and grade 3, was 29.2%.

Survival of Registered Patients

Median follow-up was 12 months (IQR 7–22 months) for all registered patients. Figure 2a shows the OS of all stage IV GC patients. MST was 12.0 months (95% CI 11.0–14.0 months). Figure 2b shows the OS of both the surgery group and nonsurgery group. MST in the surgery group was significantly longer than that in the nonsurgery group, viz. 53.0 months (95% CI 28.0 months to not reached) versus 11.0 months (10.0–12.0 months) ($P = 0.000$).

Predictive Factors for Curative-Intent Surgery

As the surgery group showed significantly longer survival compared with the nonsurgery group among stage IV GC patients, we analyzed the predictive factors for performing curative-intent surgery in the registered patients (Table 3). Univariate analysis showed that lymphogenous distant metastasis alone, positive lavage cytology (P0CY1) alone, serum level of carcinoembryonic antigen (CEA), neutrophil lymphocyte ratio (NLR), Glasgow prognostic score (GPS), and administration of doublet or triplet chemotherapy were predictive factors for curative-intent surgery for stage IV advanced GC patients. However, sex, age, presence of hematogenous metastasis alone, peritoneal dissemination, prognostic nutritional index (PNI),[31] and histological type had no correlation. Logistic regression analysis showed that lymphogenous metastasis alone, positive lavage cytology alone, low GPS, and administration of doublet or triplet chemotherapy were independent predictive factors for performing curative-intent surgery in stage IV GC patients.
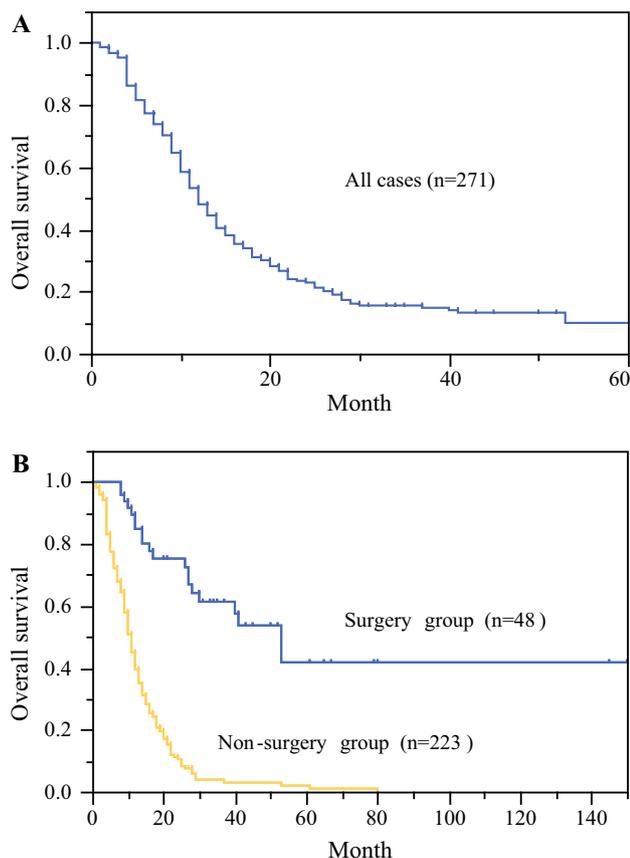
A

B

FIG. 2 Kaplan–Meier plots of OS in: **a** all stage IV gastric cancer patients (MST 12 months with 95% CI of 11.0–14.0 months), **b** stage IV gastric cancer patients who underwent curative-intent surgery (the surgery group) and patients treated by chemotherapy alone (the nonsurgery group); the surgery group showed better MST of 53.0 months (95% CI 28.0 months to NR) than the nonsurgery group (11.0 months, 95% CI 10.0–12.0 months) ($p = 0.000$). *MST* median survival time, *NR* not reached, *CI* confidence interval

Survival of Patients Who Underwent Curative-Intent Surgery

At the time of survival analysis, the median follow-up of the patients who underwent curative-intent surgery was 52 months (IQR, 25 months to not reached). There were significant differences in the OS between the R0, R1, and R2 groups ($P = 0.0002$) (Fig. 3a). The three-year survival rates were 75.4%, 33.3%, and 25.0%, respectively. Additionally, there was significant difference in DFS between the R0 and R1 groups (Fig. 3b), with 3-year DFS rates of 53.7% and 0%, respectively ($P = 0.0002$).

Prognostic Factors for OS in Patients Undergoing Curative-Intent Surgery

Univariate analysis of OS showed that ypStage IV was associated with poor OS and R0 surgery was associated with favorable OS; however, other factors, such as sex, age, distant metastatic type, and pathological response, had no significant correlation with OS (Table 4). The Cox proportional regression hazards model for OS showed that R0 surgery was an independent prognostic factor [hazard ratio (HR) 0.188, 95% CI 0.044–0.790, $P = 0.022$] (Table 4). Among the 35 patients in the R0 surgery group, 19 patients (54.3%) suffered from recurrence, with 14 patients (40.0%) showing peritoneal dissemination, 5 (14.3%) liver metastasis, 4 (11.4%) lymph node metastasis, 1 (2.9%) pleural dissemination, and 1 (2.9%) local recurrence (with overlap). There were no independent predictive factors for recurrence among the R0 surgery group (data not shown).

DISCUSSION

The results of this retrospective study show that lymphogenous distant metastasis alone, positive lavage cytology alone, low GPS, and doublet/triplet chemotherapy were predictive factors for performing curative-intent surgery for stage IV advanced GC patients, and R0 resection surgery was an independent prognostic factor for favorable long-term outcome among patients who underwent surgery.

As several studies have shown, curative-intent surgery is currently recognized as a significant factor for improving life expectancy in patients with advanced GC.[12–19,32] Yamaguchi et al.[19] reported that stage IV GC patients who underwent curative-intent surgery showed better OS than patients without surgery in every category of Yoshida's classification. Ishigami et al.[14] also reported that patients with CY1 or P1 undergoing curative-intent surgery after intraperitoneal and systemic chemotherapy showed better long-term survival than patients who did not undergo surgery. In the current study, the surgery group showed significantly longer OS than the nonsurgery group. As patients who underwent curative-intent surgery showed relatively good response to systemic chemotherapy, long-term results between the two groups showed such a difference. Although a randomized prospective study may be essentially necessary to confirm the effectiveness of curative-intent surgery, stage IV includes various kinds of statuses and the candidates for surgery are few; therefore, it is difficult to conduct a prospective trial. Thus, multiinstitutional retrospective study with a large number of patients may indicate the validity of curative-intent surgery in stage IV gastric cancer patients.

TABLE 3 Univariate and multivariate analyses for predicting curative-intent surgery for stage IV advanced gastric cancer

	Univariate		Multivariate		
	OR	p value	OR	95% CI	p value
Sex					
Male	0.546	0.077			
Female	1				
Age					
$\geq$ 75 years	0.622	0.263			
< 75 years	1				
Metastatic site					
Hematogenous	0.523	0.342			
Multiple noncurative factors	1				
Lymphogenous	2.728	0.030	3.276	1.455–7.439	0.004
Multiple noncurative factors	1		1		
Peritoneal dissemination[a]	1.690	0.253			
Multiple noncurative factors	1				
Positive lavage cytology[b]	7.502	0.007	6.394	1.476–28.80	0.014
Multiple noncurative factors	1		1		
CEA					
$\geq$ 10	0.442	0.024			
< 10	1				
NLR					
$\geq$ 4	0.489	0.050			
< 4	1				
PNI					
< 40	0.437	0.054			
$\geq$ 40	1				
GPS					
0	0.267	0.000	0.276	0.117–0.605	0.001
1/2	1		1		
Histological differentiation[c]					
G1	1.168	0.697			
G2/G3	1				
Chemotherapy					
Doublet/triplet	2.888	0.054	4.064	1.097–26.53	0.034
Monotherapy	1				

CEA carcinoembryonic antigen, *NLR* neutrophil lymphocyte ratio, *PNI* prognostic nutritional index, *OR* odds ratio, *CI* confidence interval

[a]With or without positive lavage cytology

[b]Excluding macroscopic peritoneal dissemination

[c]According to TNM classification, G1 represents well-differentiated adenocarcinoma, G2 represents moderately differentiated adenocarcinoma, and G3 represents poorly differentiated adenocarcinoma and others

Regarding predictive factors for curative-intent surgery, the results of the current study show that lymphogenous distant metastasis is mainly due to paraaortic lymph node metastasis alone, which has a high probability of undergoing curative-intent surgery. As a previous multiinstitutional phase II trial of neoadjuvant chemotherapy followed by surgery against bulky lymph node metastasis along the celiac artery and/or paraaortic lymph node metastasis (JCOG0405 study) achieved a high R0 resection rate (82%) and showed relatively good long-term survival (5-year OS rate 53%), patients with paraaortic lymph node metastasis alone can be considered as candidates for potential resection.[33] According to the previous
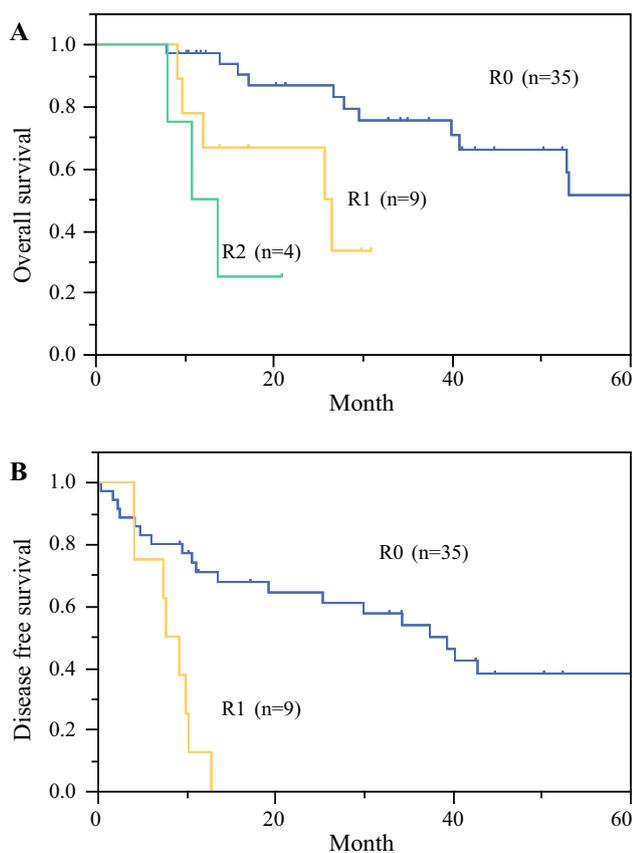
FIG. 3 Kaplan–Meier plots of overall and disease-free survival: **a** OS curves of R0, R1, and R2 surgery group; The MST (months, 95% CI) in each group was NR (40 to NR), 26.2 (9.2 to NR), and 12.3 (8.1 to NR), respectively. The three-year survival rates were 75.4%, 33.3%, and 25.0%, respectively ($p = 0.0002$). **b** Disease-free survival curves of R0 and R1 surgery group. The MST (months, 95% CI) was 37.5 (13.6 to NR) and 8.5 (4.1–10.3), respectively. The three-year survival rates were 53.7% and 0%, respectively ($p = 0.0002$). *MST* median survival time, *NR* not reached, *CI* confidence interval

study, ≤ 3 positive para-aortic lymph node metastasis will be a good indication for paraaortic lymph node dissection.[34]

Kodera et al. demonstrated that the 5-year survival rate with positive lavage cytology without macroscopic peritoneal dissemination (P0CY1) was more than 20%. Therefore, patients with P0CY1 are considered to be good candidates for curative-intent surgery in combination with perioperative chemotherapy.[35]

GPS is an inflammation-based prognostic score based on serum C-reactive protein (CRP) and albumin levels, which have been identified as useful prognostic measurements in several malignancies.[36–38] CRP elevation is the result of an increase in inflammatory cytokine levels, such as interleukin (IL)-6, IL-8, and tumor necrosis factor (TNF)-α.[39] IL-6 has been shown to increase the antiapoptotic and oncogenic potential of tumor cells, as well as induce drug resistance.[40] Hypoalbuminemia represents malnutrition

status, which has been reported as a factor that can predict treatment discontinuation and poor outcomes in patients treated at the palliative stage.[41,42] Therefore, low GPS may show good response to systemic chemotherapy and result in greater frequency of curative-intent surgery.

Since the SPIRITS trial showed the superiority of S-1 plus cisplatin doublet chemotherapy compared with S-1 monotherapy, doublet chemotherapy regimens have become a standard treatment for unresectable GC.[3] In addition, according to another phase III randomized controlled trial, capecitabine plus cisplatin plus trastuzumab regimen has become a standard chemotherapy regimen for human EGFR-related 2 (HER2)-positive unresectable GC.[2] Therefore, doublet or triplet chemotherapies have been regarded as standard therapy for unresectable GC.[2–5] In the current study, monotherapy was more often applied before 2008 as compared with after 2008 (41.4% vs. 1.6%, $P = 0.000$, data not shown). These results suggest that advancement of chemotherapy leads to high incidence of curative-intent surgery for stage IV GC.

Previously, some studies reported prognostic factors for curative-intent surgery after systemic chemotherapy in stage IV gastric cancer patients. Ishigami et al.[15] showed that R0 resection was an independent prognostic factor in 18 advanced GC cases undergoing curative-intent surgery, and Satoh et al.[18] reported that R0 or CY1 alone cases showed better survival in 44 cases with curative-intent surgery. Fukuchi et al.[43] showed that one noncurative factor and R0 resection are independent prognostic factors among patients who underwent curative-intent surgery. In the current study, R0 resection was an independent prognostic factor in patients undergoing surgery. Although further studies are necessary, R0 resection will be a strong prognostic factor for successful treatment. However, the validity of R1 surgery is still controversial. Among nine R1 resection patients, eight patients had CY1. According to the CCOG0301 study, gastric cancer patients with CY1 who underwent gastrectomy followed by adjuvant chemotherapy with S-1 for 1 year showed relatively good long-term survival (5-year OS > 25%), better than in the other stage IV gastric cancer patients.[35] Another retrospective study showed that prognosis for patients with CY0 after neoadjuvant systemic chemotherapy was significantly better than that for patients who were still CY1 after neoadjuvant systemic chemotherapy.[44] In the current study, MST of the R1 resection group was 27 months, indicating better survival time compared with other studies for stage IV GC patients undergoing chemotherapy alone. However, the validity of curative-intent surgery and best perioperative chemotherapy for this population remain uncertain.

Among patients undergoing curative-intent surgery, the R2 resection group showed the worst OS compared with the R0/R1 surgery groups. Impaired compliance with

TABLE 4 Univariate and multivariate analysis for OS in patients undergoing curative-intent surgery for stage IV advanced gastric cancer

	Univariate			Multivariate		
	MST (months)	HR	p value	HR	(95% CI)	p value
Sex						
Male	NR	1.139	0.784			
Female	53	1				
Age						
≥ 75 years	NR	0.387	0.288			
< 75 years	53	1				
Metastatic site						
Hematogenous	17	2.472	0.375			
Multiple noncurative	28	1				
Lymphogenous	NR	0.422	0.235			
Multiple noncurative	28	1				
Peritoneal dissemination	53	0.989	0.986			
Multiple noncurative	28	1				
Positive lavage cytology	31	0.713	0.693			
Multiple noncurative	53	1				
Lymph node metastasis						
ypN(+)	41	2.027	0.188			
ypN(−)	53	1				
Pathological response						
0/1a	53	0.834	0.712			
1b/2/3	53	1				
ypStage						
IV	27	2.758	0.040			
I/II/III	53	1				
Residual tumor						
R0	NR	0.184	0.002	0.188	0.044–0.790	0.022
R1/R2	26	1		1		
Adjuvant chemotherapy						
Yes	53	1.215	0.705			
No	NR	1				

MST median survival time, *NR* not reached, *HR* hazard ratio, *CI* confidence interval, *yp* pathological status after chemotherapy

chemotherapy after gastrectomy might accounted for the worse OS rather than chemotherapy per se. Thus, R2 resection should be avoided in gastrectomy cases in order not to worsen compliance with chemotherapy after surgery. In the current study, three cases with peritoneal metastasis and one case with bulky paraaortic lymph node metastasis resulted in R2 resection. Therefore, continuation of chemotherapy will be recommended for patients who have macroscopically noncurable factor on exploratory laparotomy or staging laparoscopy.

The present study has some limitations. This is a retrospective study with a relatively small sample size. However, the indication for curative-intent surgery was decided according to the patients' intent and general condition, and moreover, induction and postoperative

chemotherapeutic regimens were selected based on the trends and guidelines at that time. As a result, chemotherapeutic regimens varied during this study.

CONCLUSIONS

Patients with lymphogenous distant metastasis alone, particularly a small number of paraaortic lymph node metastases, P0CY1 alone, good immunonutritional status, and doublet/triplet chemotherapy are candidates for effective curative-intent surgery. Of these, R0 resection can provide favorable survival after surgery. As it is difficult to conduct a prospective randomized study for this population, the results of a large-scale retrospective cohort study,

CONVO-GC-1 [international retrospective cohort study of conversion therapy (adjuvant surgery) for stage IV gastric cancer 1], are anticipated.

REFERENCES

1. Ferlay JEM, Lam F, Colombet M, Mery L, Pineros M, Znaor A, Soerjomataram I, Bray F. Global cancer observatory: cancer today. Lyon, France: International Agency for Research on Cancer 2018. https://gco.iarc.fr/today.

2. Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet*. 2010; 376(9742):687–97.

3. Koizumi W, Narahara H, Hara T, et al. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. *Lancet Oncol*. 2008; 9(3):215–21.

4. Sawaki A, Ohashi Y, Omuro Y, et al. Efficacy of trastuzumab in Japanese patients with HER2-positive advanced gastric or gastroesophageal junction cancer: a subgroup analysis of the trastuzumab for Gastric Cancer (ToGA) study. *Gastric Cancer*. 2012; 15(3):313–22.

5. Yamada Y, Higuchi K, Nishikawa K, et al. Phase III study comparing oxaliplatin plus S-1 with cisplatin plus S-1 in chemotherapy-naive patients with advanced gastric cancer. *Ann Oncol*. 2015; 26(1):141–8.

6. Fujitani K, Yang HK, Mizusawa J, 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.

7. Sano T, Aiko T. New Japanese classifications and treatment guidelines for gastric cancer: revision concepts and major revised points. *Gastric Cancer*. 2011; 14(2):97–100.

8. Lordick F, Siewert JR. Recent advances in multimodal treatment for gastric cancer: a review. *Gastric Cancer*. 2005; 8(2):78–85.

9. Mahar AL, Coburn NG, Karanicolas PJ, Viola R, Helyer LK. Effective palliation and quality of life outcomes in studies of surgery for advanced, non-curative gastric cancer: a systematic review. *Gastric Cancer*. 2012; 15(Suppl 1):S138–45.

10. Shen L, Shan YS, Hu HM, et al. Management of gastric cancer in Asia: resource-stratified guidelines. *Lancet Oncol*. 2013; 14(12):e535–47.

11. Kodera Y. Surgery with curative intent for stage IV gastric cancer: is it a reality of illusion? *Ann Gastroenterol Surg*. 2018; 2(5):339–47.

12. Chan DY, Syn NL, Yap R, et al. Conversion surgery post-intraperitoneal paclitaxel and systemic chemotherapy for gastric cancer carcinomatosis peritonei. *J Gastrointest Surg*. 2017; 21(3):425–33.

13. Einama T, Abe H, Shichi S, et al. Long-term survival and prognosis associated with conversion surgery in patients with metastatic gastric cancer. *Mol Clin Oncol*. 2017; 6(2):163–6.

14. Ishigami H, Yamaguchi H, Yamashita H, Asakage M, Kitayama J. Surgery after intraperitoneal and systemic chemotherapy for gastric cancer with peritoneal metastasis or positive peritoneal cytology findings. *Gastric Cancer*. 2017; 20(Suppl 1):128–34.

15. Ishigami S, Natsugoe S, Nakajo A, et al. Salvage gastrectomy following a combination of biweekly paclitaxel and S-1 for stage IV gastric cancer. *J Gastrointest Surg*. 2008; 12(8):1370–75.

16. Mieno H, Yamashita K, Hosoda K, 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.

17. Sato Y, Ohnuma H, Nobuoka T, 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.

18. Satoh S, Okabe H, Teramukai 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.

19. Yamaguchi K, Yoshida K, Tanahashi T, et al. The long-term survival of stage IV gastric cancer patients with conversion therapy. *Gastric Cancer*. 2018; 21(2):315–23.

20. 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.

21. Japanese Gastric Cancer A. Japanese classification of gastric carcinoma: 3rd English edition. *Gastric Cancer*. 2011; 14(2):101–12.

22. Japanese Gastric Cancer A. Japanese classification of gastric carcinoma: 2nd English Edition. *Gastric Cancer*. 1998; 1(1):10–24.

23. Sakata Y, Ohtsu A, Horikoshi N, et al. Late phase II study of novel oral fluoropyrimidine anticancer drug S-1 (1 M tegafur-0.4 M gimestat-1 M otastat potassium) in advanced gastric cancer patients. *Eur J Cancer*. 1998; 34(11):1715–20.

24. Koizumi W, Kim YH, Fujii M, et al. Addition of docetaxel to S-1 without platinum prolongs survival of patients with advanced gastric cancer: a randomized study (START). *J Cancer Res Clin Oncol*. 2014; 140(2):319–28.

25. Kunisaki C, Takahashi M, Makino H, et al. Phase II study of biweekly docetaxel and S-1 combination chemotherapy as first-line treatment for advanced gastric cancer. *Cancer Chemother Pharmacol*. 2011; 67(6):1363–68.

26. Kunisaki C, Takahashi M, Nagahori Y, et al. Phase I study of biweekly docetaxel and S-1 combination chemotherapy for advanced gastric cancer. *Anticancer Res*. 2008; 28(4c):2473–78.

27. Takahari D, Mizusawa J, Koizumi W, Hyodo I, Boku N. Validation of the JCOG prognostic index in advanced gastric cancer using individual patient data from the SPIRITS and G-SOX trials. *Gastric Cancer*. 2017; 20(5):757–63.

28. Sato K, Kunisaki C, Kosaka T, et al. Multicenter phase II study of capecitabine plus cisplatin as first-line therapy for human epidermal growth factor receptor 2-negative advanced gastric cancer: Yokohama Clinical Oncology Group Study YCOG1107. *Cancer Chemother Pharmacol*. 2017; 80(5):939–43.

29. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004; 240(2):205–13.

30. Association JGC. Japanese gastric cancer treatment guidelines 2018 (ver. 5)2018.

31. Onodera T, Goseki N, Kosaki G. [Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients]. *Nihon Geka Gakkai Zasshi*. 1984; 85(9):1001–5.

32. Terashima M. Conversion therapy for gastric cancer: who can make conversion as successful as Goromaru? *Gastric Cancer*. 2016; 19(3):685–6.

33. Tsuburaya A, Mizusawa J, Tanaka Y, 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.

34. Kunisaki C, Shimada H, Yamaoka H, et al. Indications for paraaortic lymph node dissection in gastric cancer patients with paraaortic lymph node involvement. *Hepatogastroenterology*. 2000; 47(32):586–9.

35. Kodera Y, Ito S, Mochizuki Y, et al. Long-term follow up of patients who were positive for peritoneal lavage cytology: final report from the CCOG0301 study. *Gastric Cancer*. 2012; 15(3):335–7.

36. Forrest LM, McMillan DC, McArdle CS, Angerson WJ, Dunlop DJ. Comparison of an inflammation-based prognostic score (GPS) with performance status (ECOG) in patients receiving platinum-based chemotherapy for inoperable non-small-cell lung cancer. *Br J Cancer*. 2004; 90(9):1704–6.

37. Kimura J, Kunisaki C, Makino H, et al. Evaluation of the Glasgow Prognostic Score in patients receiving chemoradiotherapy for stage III and IV esophageal cancer. *Dis Esophagus*. 2016; 29(8):1071–80.

38. Kunisaki C, Takahashi M, Ono HA, et al. Inflammation-based prognostic score predicts survival in patients with advanced gastric cancer receiving biweekly docetaxel and s-1 combination chemotherapy. *Oncology*. 2012; 83(4):183–91.

39. Miki C, Konishi N, Ojima E, et al. C-reactive protein as a prognostic variable that reflects uncontrolled up-regulation of the IL-1-IL-6 network system in colorectal carcinoma. *Dig Dis Sci*. 2004; 49(6):970–6.

40. Jee SH, Shen SC, Chiu HC, Tsai WL, Kuo ML. Overexpression of interleukin-6 in human basal cell carcinoma cell lines increases anti-apoptotic activity and tumorigenic potency. *Oncogene*. 2001; 20(2):198–208.

41. Andreyev HJ, Norman AR, Oates J, Cunningham D. Why do patients with weight loss have a worse outcome when undergoing chemotherapy for gastrointestinal malignancies? *Eur J Cancer*. 1998; 34(4):503–9.

42. Sato S, Kunisaki C, Suematsu H, et al. Impact of sarcopenia in patients with unresectable locally advanced esophageal cancer receiving chemoradiotherapy. *In Vivo*. 2018; 32(3):603–10.

43. Fukuchi M, Ishiguro T, Ogata K, et al. Prognostic role of conversion surgery for unresectable gastric cancer. *Ann Surg Oncol*. 2015; 22(11):3618–24.

44. Yamamoto M, Kawano H, Yamaguchi S, et al. Comparison of neoadjuvant chemotherapy to surgery followed by adjuvant chemotherapy in japanese patients with peritoneal lavage cytology positive for gastric carcinoma. *Anticancer Res*. 2015; 35(9):4859–63.