

## Preoperative Chemotherapy with S-1 and Cisplatin for Highly Advanced Gastric Cancer

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**Abstract.** *Feasibility and efficacy of S-1 and cisplatin followed by surgery was evaluated, and factors contributing to survival benefit were analyzed. Patients and Methods: In total, 120 consecutive patients with highly advanced gastric cancer were treated with S-1 (80 mg/m<sup>2</sup> for 21 consecutive days) and cisplatin (50 mg/m<sup>2</sup> on day 8). Results: The response rate was 62.5% overall, and 75.7% for these with metastatic lymph nodes. Grade 3/4 adverse events were less than 10%. The median survival time was 41.9 months among 93 patients whose primary lesion was resected. Liver metastasis, R2 resection, poor performance status and lack of response were identified as independent risk factors by a multivariate analysis. Conclusion: Preoperative chemotherapy with S-1 and cisplatin was effective. The results show the need for different approaches in the treatment of patients with metastases and these without.*

The only curative treatment for gastric adenocarcinoma is R0 resection, arguably accompanied by D2 lymph node dissection according to the Guidelines of the Japanese Gastric Cancer Association (JGCA) (1). Local control is considered an essential component of the treatment for gastric carcinoma, and extended lymphadenectomy can accomplish this task safely in experienced hands (2). The prognosis for stage III/IV advanced gastric cancer (AGC) remains unsatisfactory, however, and further improvement in surgical technique is unlikely to lead to notable progress in the outcome (3-4). Hence the development of an effective multimodal strategy has been sought after by various study groups.

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A recent meta-analysis performed in the West showed that combination regimens achieve better survival outcomes than those with 5-fluorouracil (5-FU) monotherapy and that regimens containing 5-FU, anthracyclines and cisplatin (CDDP) are the most effective (5). A perioperative chemotherapy using this triplet was actually found to improve survival of potentially curable AGC significantly when compared with treatment by surgery alone (6). Downstaging and eradication of micrometastases through the preoperative chemotherapy component may have had a particularly important role in such a strategy. In Japan, postoperative adjuvant chemotherapy by S-1, a dehydropyrimidine dehydrogenase-inhibiting 5-FU derivative, was found to improve survival of patients with curatively resected stage II/III gastric cancer. Addition of adequate preoperative therapy to this strategy may enhance the survival of patients with resectable AGC, while downstaging through preoperative chemotherapy may provide patients with more advanced cancer some chance for cure. One candidate for use is intensive preoperative chemotherapy under such circumstances would be a combination of S-1 and CDDP, which led to a response rate of 54% and median survival time of 13 months among patients with unresectable gastric cancer in a phase III trial (7). This combination was also shown to be feasible as a preoperative induction therapy in a case series involving a smaller number of patients (8).

In the current study, 120 consecutive AGC patients who were treated with S-1/CDDP therapy prior to surgery were retrospectively analyzed to assess the efficacy and safety of this combination as a preoperative therapy and to identify the subset of patients who may benefit from this strategy.

### Patients and Methods

**Patients.** The files for one hundred and twenty consecutive patients with primary AGC who were treated preoperatively by a combination of S-1 and CDDP between October 2000 and December 2005 were retrieved from the prospective database of Niigata Cancer Center according to the following criteria: histologically confirmed adenocarcinoma of the stomach; clinically diagnosed as locally

advanced T3/T4-stage disease or metastatic disease; evaluable lesions on computed tomography (CT) scan, at upper gastrointestinal series and/or upper digestive endoscopies; age less than 75 years; ECOG performance status between 0 and 2; no prior chemotherapy or radiotherapy; sufficient organ functions represented by leukocyte count of more than  $3,000/\text{mm}^3$ , platelets more than  $10 \times 10^4/\text{mm}^3$ , GOT/GPT less than 2 times the upper limit of normal range (ULN), total bilirubin less than 2.0 mg/dl, BUN and creatinine less than the ULN; no serious co-morbidities; no concurrent active malignancy; no serious psychosomatic disorder; and provision of written informed consent. Staging laparoscopy was performed only for patients with linitis plastica or those with macroscopically type 3 cancer with preoperatively estimated diameter of  $>8$  cm. Cytological examination of the peritoneal washes was performed at the time of staging laparoscopy, but the result was used only as a reference, and detection of cancer cells in this examination did not preclude patients from receiving preoperative chemotherapy followed by surgery.

**Treatment schedule.** All patients received systemic chemotherapy consisting of S-1 and CDDP. S-1 was orally administered at a dose of  $80 \text{ mg/m}^2$  for 21 consecutive days, followed by 14 days of rest. With the intent to deliver the treatment on an outpatient basis, the dose of CDDP was modified from the original version by Koizumi *et al.* in which  $60 \text{ mg/m}^2$  had been administered. CDDP was administered intravenously on day 8 at a dose of  $50 \text{ mg/m}^2$ . The treatment was repeated every 5 weeks. Patient status was evaluated after each course of the treatment. Toxicity was assessed using the National Cancer Institute-Common Toxicity Criteria version 3.0. The response of measurable lesions was evaluated according to the RECIST criteria. The primary lesion, when not considered as measurable by the RECIST criteria, was assessed according to the Japan Gastric Cancer Association (JGCA) clinical criteria for response assessment of chemotherapy and radiotherapy. The assessment was based on shrinkage and morphological change of the primary tumor as evaluated by barium contrast study and/or endoscopic examinations (9).

Patients with locally advanced cancer were treated by chemotherapy until primary cancer or massive nodal metastases responded and resection with curative intent was deemed possible. Patients with metastatic cancer (those with hepatic or peritoneal metastases) were treated until metastatic lesions achieved complete response by CT or became co-resectable. Patients who remained with clear evidence of unresectable disease and those who did not respond to the chemotherapy were discouraged from receiving surgery. Surgery with intent to cure was performed at least 3 weeks after the final cycle. Most patients were treated by S-1 monotherapy as an adjuvant therapy after surgery. Treatments after R2 resection or at detection of recurrent disease were decided at the discretion of each physician.

**Study design and statistical analysis.** Median survival time (MST) was calculated from the initiation of chemotherapy to death or the day when the patient was last interviewed. Survival curves were calculated by the Kaplan-Meier method and compared by the log-rank test. Univariate and multivariate analyses using Cox's proportional hazards model was performed to identify independent prognostic factors. All statistical calculations were performed using statistical analysis system (SAS) version 8.2 (IBM, North Caroline, USA) and a value of  $p < 0.05$  was considered as statistically significant.

## Results

**Patient demographics.** Characteristics of the 120 patients are shown in Table I. There were 75 men and 45 women with a median age of 61 years (range 29 to 83 years). There were 44 patients with linitis plastica type cancer (36.7%). Non-curative factors included liver metastasis in 8 patients, peritoneal dissemination in 30, involvement of abdominal para-aortic lymph nodes in 34 and locally advanced and potentially unresectable gastric cancer in 12. The pretreatment clinical stage (c-stage) was diagnosed according to the classification of JGCA, which was based on the findings of CT, upper GI series, endoscopy, and staging laparoscopy. Preoperative stages were decided according to the JGCA staging system (c-stage II: 1 case; c-stage III: 33 cases; c-stage IV: 86 cases). Distribution of the c-stage IV factors was as follows: metastasis to the paraaortic nodes in 34 cases, cT4N2 in 12 cases, hepatic metastasis in 8 cases, peritoneal dissemination in 30 cases, and other distant metastasis in 4 cases.

**Proportion of the treatment performed at outpatient clinic.** The median number of administered courses was 3 (range: 1-7), and the proportion of care given in the outpatient setting was 86%. Forty-seven patients who underwent staging laparoscopy were admitted for the procedure and given the first course of chemotherapy during the same stay in the hospital. Of the 73 remaining patients, 22 managed to receive chemotherapy entirely on an outpatient clinic basis. However, the rest of the patients needed admission for hydration and antiemetic therapy during administration of CDDP.

**Surgery.** After chemotherapy, 27 patients failed to be treated by surgery, mostly because of persistence of metastatic disease through imaging studies. The remaining 93 patients underwent surgery and gastrectomy was performed in all patients. The overall resection rate was 77.5%. The surgical procedure was total gastrectomy in 57 patients and distal gastrectomy in 36 patients. R0 resection was possible in 68 patients (73.1% of all patients who underwent surgery), of whom 25 received combined resection of the involved adjacent organs and 14 underwent extended lymph node dissection including of the para-aortic lymph nodes. Of those who underwent surgery, there were 59 males and 34 females, with a median age of 61 years (range: 29 to 77 years) (Table II). The median hospital stay was 18 days. The median duration of surgery was 195 minutes and the median blood loss was 225 ml. The distribution of postoperative c-stage was as follows; 26 patients in c-stage I/II, 26 in c-stage III, and 41 in c-stage IV. R0 resection was successfully performed in 68 (73.1%) patients. Downstaging was obtained in 32 (34.4%) patients.

**Clinical response to chemotherapy.** The objective response of the evaluable lesions is shown in Table III. The overall

Table I. Patient characteristics (N=120).

Variable		No. of cases
Age, years median (range)	61.0 (29-83)	
Gender	Male/female	75/45
Performance status	0/1/2	80/26/14
Location	L/M/U/LMU	18/33/37/32
T stage	T3/T4	108/12
Metastasis		
Lymph node	N3/N1,2/N0/?	34/72/5/9
Liver	H0/H1	112/8
Peritoneum	P0/P1	90/30
Gross type	Type 2, 3/type 4	76/44
Histological type	Diff./undiff.	44/76
Clinical stage	II,III/IV	34/86

? unknown; L, lower; M, middle; U, upper.

Table II. Patient characteristics of resected cases.

Variable		No. of cases
Gender	Male/female	59/34
Age, years	median (range)	61.0 (29-77)
Hospital stay (days)	median (range)	18 (13-198)
Duration of operation (min)	median (range)	195 (90-367)
Bleeding vol. (ml)	median (range)	225 (20-1510)
Surgical procedure	DGR/TGR	36/57
LN dissection	D1/D2/D3	16/63/14
Depth of tumor invasion (T)	T1,2/T3/T4	11/57/25
Lymph node metastasis (N)	N0,N1/N2/N3	42/34/17
Pathological stage	I-II/III/IV	26 /26 /41
Curability	CA, CB/CC	68/25
Histological effect (Grade)	1a /1b/2/3	46/28/18/1

N=93; resection rate 77.5%. DGR, distal gastrectomy; TGR, total gastrectomy; D1, dissection of all the group 1 nodes; D2, dissection of all the group 1 and 2 nodes; D3, dissection of all the group 1, group 2 and group 3 nodes; CA, no residual disease with high probability of cure; CB, no residual disease but not fulfilling criteria for CA; CC, definite residual disease; Grade, grading due to the proportion of degeneration area in the tumor by the Japanese Classification of Gastric Carcinoma; (1a, the proportion of degeneration area in the tumor is less than 1/3; 1b, 1/3-2/3; 2, more than 2/3; 3, no viable tumor cell).

response rate (ORR) was 62.5% (95% confidence interval (CI): 53.8-71.2%). There were 75 responders (one complete response (CR) and 74 partial responses (PR)), when the response to the primary lesion was disregarded. Response rate for regional/para-aortic lymph nodes, primary gastric tumor (assessed based on JGCA clinical criteria for response assessment of chemotherapy and radiotherapy), liver metastases and peritoneal metastases was 75.7% (56/74), 61.7% (74/120), 28.6% (2/7) and 23.8% (5/21), respectively.

Table III. Response.

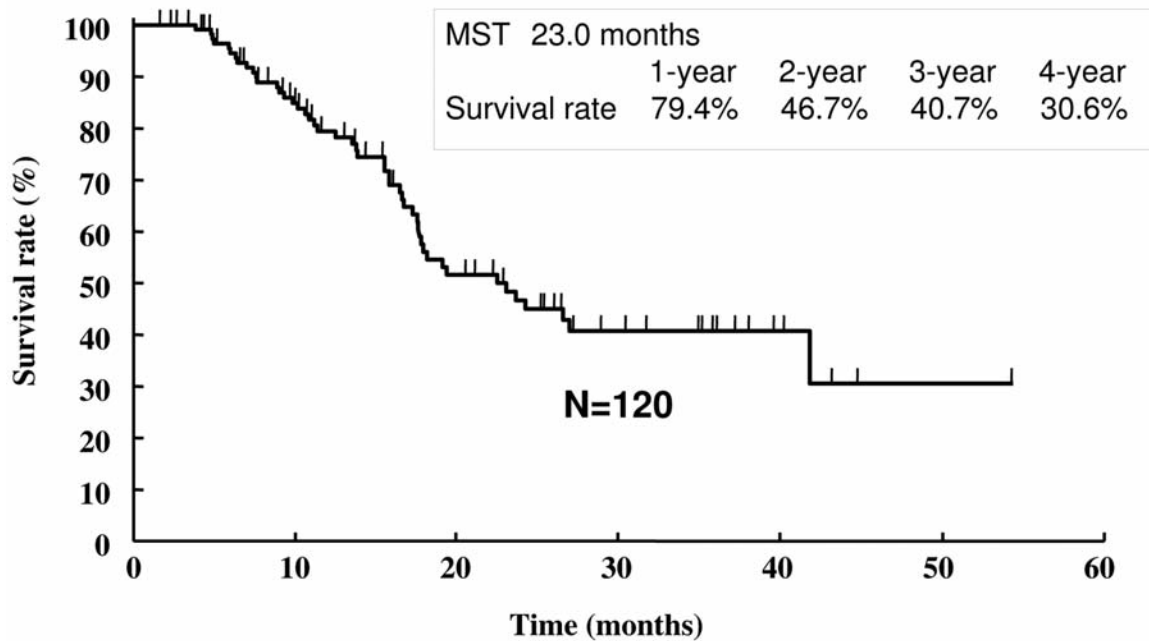
	No. of cases	CR	PR	NC	PD	ORR (%)
Overall	120	1	74	42	3	62.5
Primary lesion	120	2	72	45	1	61.7
Metastatic lesions						
Lymph nodes	74	4	52	18	0	75.7
Liver	7	1	1	5	0	28.6
Peritoneum	*21	0	5	14	2	23.8
Other	**4	0	0	3	1	0.0

\*CY1→CY0 (9 cases); \*\*lung and pleura, ovary ×3. CY, peritoneal cytology; CY0, benign and/or indeterminate cells on peritoneal cytology; CY1, cancer cells on peritoneal cytology.

Table IV. Toxicity.

	NCI-CTC Grade				Overall (%)	Grade 3/4 (%)
	1	2	3	4		
<b>Hematological</b>						
Leucopenia	24	27	1	0	43.3	0.8
Neutropenia	27	31	9	0	55.8	7.5
Anemia	35	36	7	1	65.0	6.7
Thrombocytopenia	36	8	5	3	40.8	6.7
Creatinine	11	0	0	0	9.2	0.0
Total bilirubin	3	3	0	0	5.0	0.0
GOT/GPT	12	5	0	0	15.3	0.0
<b>Non-hematological</b>						
Anorexia	51	23	7	0	67.5	5.8
Nausea	51	14	3	0	56.7	2.5
Vomiting	18	6	0	0	20.0	0.0
Diarrhea	18	1	2	0	17.5	1.7
Constipation	2	1	0	0	2.5	0.0
Stomatitis	23	3	0	0	21.7	0.0
Taste disturbance	30	2	0	0	26.7	0.0
Hand-foot skin reaction	16	0	0	0	13.3	0.0
Pigmentation	47	5	0	0	43.3	0.0
Nail changes	30	0	0	0	25.0	0.0
Alopecia	10	0	0	0	8.3	0.0
General fatigue	26	7	1	0	28.3	0.8
Gastric ulcer	0	0	1	1	1.7	1.7

Twenty-five other patients (42.4%) had stable disease (SD), and only 2 patients had progressive disease (PD). Pathologic CR of the metastatic lymph nodes, including para-aortic lymph nodes, was confirmed after surgery in 4 patients. Of the 75 responders, residual tumor was completely resected in 51 (68.0%). Out of the 47 patients who underwent staging laparoscopy, 31 were found to have peritoneal metastasis; of these, complete remission of the peritoneal disease was confirmed at surgery in 9 (29.0%).



**MST, median survival time**

Figure 1. Cumulative probability of overall survival as estimated by the Kaplan-Meier method in 120 patients. The median survival time was 23.0 months, and a 4-year survival rate was 30.6%.

**Toxicity.** The adverse reactions during 308 cycles of S-1/CDDP regimen were evaluated according to NCI-CTC grade (Table IV). The most frequent toxicities of S-1/CDDP were myelosuppression and gastrointestinal symptoms. The incidence of notable adverse events were 55.8% for neutropenia, 43.3% for leukocytopenia, 65.0% for anemia 65.0%, 40.8% for thrombocytopenia, 67.5% for anorexia, 56.7% for nausea, respectively. However the incidence of grade 3/4 toxicity was infrequent: neutropenia 7.5%, leucopenia 0.8%, anemia 6.7%, thrombocytopenia 6.7%, anorexia 5.8% and nausea 2.5%. The preoperative chemotherapy was generally well tolerated. There was no surgical mortality, and postoperative surgical morbidity was remarkably low at 17.2%.

**Survival and analysis of prognostic factors.** The median survival time of patients overall was 23.0 months, with a 4-year survival rate of 30.6% (Figure 1). The median survival time of patients who went on to receive surgery was 41.9 months (95% CI: 31.9-51.9 months) and the 3-year survival rate was 51.2% (95% CI: 37.4-64.9%) (Figure 2). There was a statistically significant difference in survival between these patients and these who failed to receive gastrectomy.

For all patients, response to chemotherapy, location of the tumor, resectability of the primary lesion, liver metastasis, and peritoneal metastasis were predictive of the overall survival (Table V). In the multivariate analysis, response to

chemotherapy, peritoneal metastasis and hepatic metastasis were the only independently prognostic factors (Table VI).

For the patients who were treated by gastrectomy, curability of surgery, response to the chemotherapy, hepatic metastasis, peritoneal metastasis, the extent of lymph node dissection, N category, and performance status were identified as significant prognostic determinants (Table VII). Of these, hepatic metastasis, curability of surgery, performance status and response to the chemotherapy were identified as independent prognostic factors (Table VIII).

**Discussion**

Gastric carcinoma remains a major health problem worldwide, primarily because it is often diagnosed at an advanced stage. In addition, it often relapses even after a potentially curative resection, and multimodal treatments have been sought after by various study groups to combat residual micrometastases. One of the consequences is that postoperative chemoradiation was found to significantly improve outcome of curatively resected patients and has become a standard of care in North America (10-11). There is a suspicion, however, that radiation as a local therapy may have compensated for poor local control due to suboptimal surgery, and the Japanese surgeons remained confident that extended nodal dissection precludes the need for adjuvant

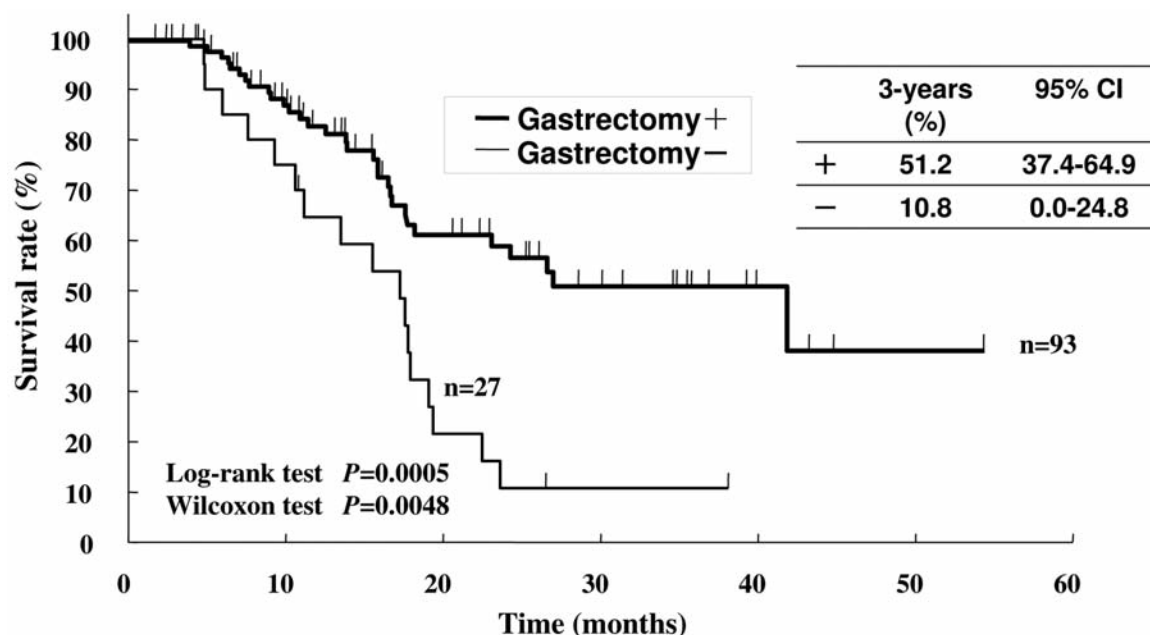


Figure 2. Cumulative probability of survival in the gastrectomy group (93 patients) and the non-gastrectomy group (27 patients) as estimated by the Kaplan-Meier method. A 3-year survival rate of the former and the latter was 51.2% and 10.8%, respectively. There was a statistically significant difference.

treatment focused around the gastric bed. However, the Japanese experts felt promise when S-1, a novel oral fluoropyrimidine derivative, became available. This drug achieved a response rate of more than 40% when used as a single agent (12-13), while the response rate rose to 50-75% when used in combination with CDDP (12), irinotecan (14-15), docetaxel (17-18), and paclitaxel (19-20). Their expectations were met when an interim analysis of a pivotal phase III study revealed that postoperative adjuvant chemotherapy with single agent S-1 significantly improved survival of stage II-III gastric cancer patients when compared with surgery alone (21).

Gastrectomy causes various gastrointestinal symptoms and nutritional deficits, and additive toxicity through postoperative chemotherapy could be a substantial burden for the patients. More than 10% of the Japanese patients in the aforementioned phase III trial had actually failed to continue with oral S-1 at three month postoperatively. Post-gastrectomy deterioration of compliance regarding chemotherapy was also observed in the British MAGIC trial, in which 88% of patients received preoperative chemotherapy whereas only 55% tolerated the same therapy postoperatively (6). Thus, there is a rationale for delivery of a somewhat toxic but effective chemotherapy preoperatively, and neoadjuvant chemotherapy is a promising option for resectable AGC. In addition, the indication for preoperative chemotherapy could be extended to include AGC with synchronous metastases, provided the metastatic lesions are co-resectable or become resectable after chemotherapy.

Table V. Univariate analysis of 120 patients with primary AGC who were treated preoperatively by a combination of S-1 and CDDP (log-rank test).

Variable		P-value
Response due to JCGC	(PR/NC,PD)	<0.0001
Location	(L,M,U/LMU)	0.0068
Surgery	(+/-)	0.0005
Liver metastasis	(H0/H1)	<0.0001
Peritoneal metastasis	(P0/P1)	0.0002
Gender	(Female/male)	0.1521
Histological type	(Diff./undiff.)	0.3697
Gross type	(Type 2,3/type 4)	0.0815
T stage	(T1, T2/T3, T4)	0.0826
Lymph node metastasis	(N0, N1/N2, N3)	0.4623
Age	(≤59 vs. 60+)	0.6489
PS	(0/1, 2)	0.1154

JCGC, Japanese classification of gastric cancer; PR, partial response; NC, no change; PD, progressive disease; PS, performance status according to the WHO criteria.

Although chemotherapy is the standard of care for metastatic gastric cancer, it does not cure the disease. One can argue therefore that surgery remains an option as a part of multimodal therapy for patients with resectable metastases. When such is the case, preoperative chemotherapy provides useful information as regards drug sensitivity and biology of

Table VI. Multivariate analysis of 120 patients with primary AGC who were treated preoperatively by a combination of S-1 and CDDP. Cox's proportional hazard model (SAS ver. 8.2, score method).

Variable	Hazard ratio	95% Confidence limits	P-value
Liver metastasis (H0/H1)	8.142	(1.446-5.586)	<0.0001
Response (CR,PR/NC,PD)	2.842	(1.300-5.149)	0.0025
Peritoneal metastasis (P0/P1)	2.587	(3.459-19.162)	0.0068

CR, complete response; PR, partial response; NC, no change; PD, progressive disease.

cancer, besides the potential to downstage the disease, and prevents futile surgery for cancer that is destined for rapid progression. In either of the settings, efficacy along with safety of preoperative chemotherapy and its influence on surgery that follows need to be addressed.

Chemotherapeutic regimens with high response rates are required to achieve downstaging along with eradication of micrometastases whilst preventing disease progression. In due course, a combination of S-1 and CDDP has become acknowledged in Japan as a candidate for neoadjuvant chemotherapy owing to its remarkable response rate, in excess of 70%, and this is the regimen with which the authors chose to treat AGC patients preoperatively. A combination of S-1 and CDDP was first established by Koizumi *et al.*, by which 60 mg/m<sup>2</sup> of CDDP was to be administered on day 8 of a 5-week course. Administration at this dosage was feared to cause nausea and potential damage to renal function, and patients usually had to be admitted for a few days for continuous intravenous infusion along with extensive use of antiemetics. To lower the risk of organ dysfunction prior to surgery and in an attempt to deliver all the drugs on an outpatient basis, we modified the dose of CDDP to 50 mg/m<sup>2</sup>. Consequently, CDDP was delivered entirely on the outpatient basis in 22 out of 73 patients, but admission was still necessary for all remaining patients. Response rate for the nodal metastases was satisfactory at over 70%, but those for other metastatic lesions were substantially lower. Given that the number of beds available for preoperative chemotherapy is limited, establishment of a modified regimen with further dose reduction, perhaps through an increase in the number of intravenous deliveries per cycle to preserve the dose intensity, may be warranted.

Response to the chemotherapy is undoubtedly a valuable parameter in deciding whether or not to proceed to surgery for metastatic cancer. When chemotherapy is performed in the neoadjuvant setting, however, cancer is usually resectable before the treatment. The response will then have to be evaluated even more cautiously and diligently to avoid delay in surgery when the cancer is not responding to the

Table VII. Univariate analysis of 93 patients underwent gastrectomy after chemotherapy (log-rank test).

Variable		P-value
Curability	(CA,CB/CC)	<0.0001
Liver metastasis	(H0/H1)	0.0001
Response	(PR/NC,PD)	0.0026
Peritoneal metastasis	(P0/P1)	0.0119
LN dissection	(D1/D2,3)	0.0164
Lymph node metastasis	(N0,1/N2,3)	0.0251
PS	(0/1,2)	0.0352
Gender	(Male/female)	0.0781
Location	(LMU/L,M,U)	0.1020
Age	(<59 vs. 60+)	0.2040
Gross type	(Type 2,3/type 4)	0.2577
cT stage	(T1,2/T3,4)	0.5851
Histological type	(Diff./undiff.)	0.9282

CA, no residual disease with high probability of cure; CB, no residual disease but not fulfilling criteria for CA; CC, definite residual disease; D1, dissection of all the group 1 nodes; D2, dissection of all the group 1 and 2 nodes; D3, dissection of all the group 1, group 2 and group 3 nodes.

Table VIII. Multivariate analysis of 93 patients underwent gastrectomy after chemotherapy. Cox's proportional hazard model. (SAS ver. 8.2, score method).

Variables	Hazard ratio	95% confidence limits	P-value
fH (0/1)	6.308	(2.145-18.553)	0.0008
Curability (A,B/C)	3.608	(1.610-8.085)	0.0018
PS (0/1,2)	2.856	(1.308-6.234)	0.0084
Response (CR,PR/NC,PD)	2.585	(1.155-5.787)	0.0209

CA, no residual disease with high probability of cure; CB, no residual disease but not fulfilling criteria for CA; CC, definite residual disease; CR, complete response; PR, partial response; NC, no change; PD, progressive disease.

chemotherapy. When the tumor is not accompanied by distant metastasis or bulky lymphadenopathy, the primary lesion would be the only target for evaluating response. In addition, shrinkage of the primary may allow surgeons to avoid total gastrectomy in cases of advanced cancer of the distal or mid-portion of the stomach. Thus, the Authors insisted on assessing response in the primary lesion according to the Japanese criteria, although these lesions are not considered as measurable by the RECIST criteria. Marked response to the primary was observed in 61.7% of the patients.

In the current population of advanced/metastatic cancer, the R0 resection rate among those who eventually underwent surgery was unexpectedly high at 73.1%. The MST was 23

months overall and 42 months among those who underwent surgery. The combination of S-1 and CDDP thus provided promising survival data with a favorable toxicity profile with no treatment-related deaths. Multivariate analysis of all patients identified peritoneal metastasis and hepatic metastasis as independent prognostic factors in all patients. Of patients with metastatic cancer, only those with hepatic metastasis that responded to chemotherapy went on to receive surgery. Nevertheless, hepatic metastasis remained an independent prognostic factor among those who underwent surgery. These results confirm that the outcome of patients with metastatic cancer is quite different from those with locally advanced cancer (those who undergo so-called neoadjuvant chemotherapy). In future, these two groups of patients should thus be treated by different strategies and analyzed independently.

## Conclusion

S-1/CDDP at a reduced dose was safe and feasible when given preoperatively, without notable influence over the surgical morbidity. It remained effective against the primary tumor and nodal metastases. The survival benefit of cytoreductive surgery in metastatic cancer that responds to such chemotherapy needs to be addressed by a randomized trial, while another trial is needed to confirm its benefit in the neoadjuvant setting for locally advanced cancer.

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