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/mm^3, platelets more than 10×10^4/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 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 mg/m^2 had been administered. CDDP was administered intravenously on day 8 at a dose of 50 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 plastic 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).

Table III. *Response.*

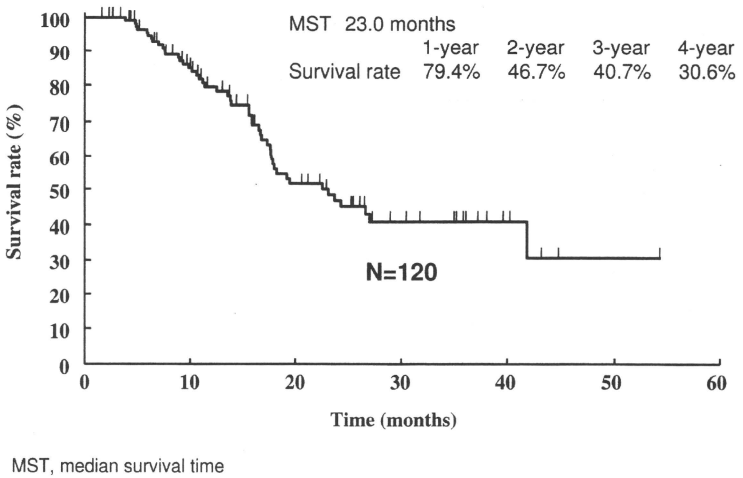
	No. of cases	CR	PR	NC	PD	ORR (%)
Overall	120	1	74	42	3	62.5
Primary lesion	120	2	72	45	1	61.7
Metastatic lesions						
Lymph nodes	74	4	52	18	0	75.7
Liver	7	1	1	5	0	28.6
Peritoneum	*21	0	5	14	2	23.8
Other	**4	0	0	3	1	0.0

*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					
	1	2	3	4	Overall (%)	Grade 3/4 (%)
Hematological						
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
Non-hematological						
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

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. 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

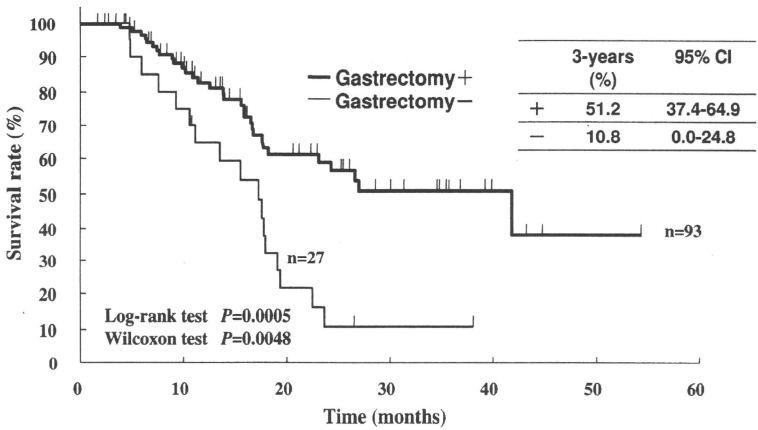


Figure 2. *Cumulative probability of survival in the gastrectomy group (93 patients) and the non-gastrectomy group (27 patients) as estimated by the Kaplan-Meier method. A 3-year survival rate of the former and the latter was 51.2% and 10.8%, respectively. There was a statistically significant difference.*

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.

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.

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^2 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^2. 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 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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A phase II study of preoperative chemotherapy with S-1 plus cisplatin followed by D2/D3 gastrectomy for clinically serosa-positive gastric cancer (JACCRO GC-01 study)

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Abstract

Aims: Clinically serosa-positive (T3–4) gastric cancer has a poor prognosis. This phase II trial explored the feasibility and safety of preoperative chemotherapy followed by D2 or D3 gastrectomy in this type of gastric cancer.
Methods: Patients with T3–4 gastric cancer received one course of S-1 (80 mg/m^2 daily for 3 weeks) and cisplatin (60 mg/m^2 on day 8) chemotherapy and then underwent D2 or D3 gastrectomy with curative intent. Primary endpoint was toxicities.
Results: Of 50 patients enrolled, 49 were eligible and received the treatment protocol. Chemotherapy-related toxicities were mild; grade 3 neutropenia in 2 patients, anorexia in 3, and nausea in 2, and no grade 4 toxicities. Clinical response was achieved in 13 of 34 evaluable patients. Of the 49 patients, 39 underwent D2 or D3 dissection. There was no surgical mortality. Operative morbidity occurred in 5 of 49 patients, including pancreatic fistula in 1 and abdominal abscess in 2.
Conclusion: This multi-modality treatment seems to be feasible and safe for T3–4 gastric cancer.

Keywords: Gastric cancer; Chemotherapy; Surgery; Phase II

Introduction

Gastric cancer remains the second leading cause of cancer death in the world and is the most frequent malignancy in Japan, South America, and Eastern Europe.[1] Complete resection is essential for cure,[2] and because more than half of T3 and T4 tumors have metastasized to lymph nodes along the major branch arteries or in the para-aortic area, complete resection has involved D2 or D3 dissection in Japan.[3,4] However, despite resection of these tumors with curative intent, prognosis has been limited.[5] To improve the survival of these patients, new treatment strategies must be developed.

Most clinical trials of postoperative adjuvant chemotherapy have failed to prove a survival benefit.[6] However, a large phase III trial recently demonstrated that adjuvant chemotherapy with S-1 (1 M tegafur–0.4 M gimestat–1 M ostat potassium) significantly improved survival after D2 curative

Abbreviations: CF, 5-FU plus cisplatin; ECF, triplet chemotherapy of CF plus epirubicin; DCF, CF plus docetaxel; JACCRO, Japan Clinical Cancer Research Organization; WBC, white blood cell count; PLT, platelet count; GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; ALP, alkaline phosphatase; RECIST, response evaluation criteria in solid tumors; JCOG, Japan Clinical Oncology Group.

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gastrectomy in Japanese patients with T2N+ or T3 disease.[7] Based on this, D2 surgery and postoperative S-1 chemotherapy has been established as a standard treatment in Japan. Nonetheless, even with adjuvant S-1 chemotherapy, the prognosis for T3 tumors was not satisfactory.

Preoperative chemotherapy followed by extended surgery has some theoretical benefits when compared with postoperative chemotherapy.[8] If bulky tumors are reduced in size by chemotherapy, complete tumor removal could theoretically be easily achieved by extended surgery. If distant micrometastases are eliminated by chemotherapy, complete resection by extended surgery may improve survival and result in cure in some cases. However, preoperative chemotherapy followed by extended surgery has not been confirmed in phase III trial.

A high response rate and relatively low toxicity are required for preoperative chemotherapy, because target tumors are resectable or marginally resectable and the patients must receive potentially curative surgery after chemotherapy. Combined chemotherapy with S-1 plus cisplatin is an attractive regimen for preoperative chemotherapy for gastric cancer. A previous phase II trial of this regimen in metastatic gastric cancer reported a high response rate of 76% and acceptable toxicities.[9] Recently, a Japanese phase III trial of chemotherapeutic regimens for metastatic gastric cancer (SPIRITS trial) demonstrated that S-1 plus cisplatin led to significantly longer median overall survival than S-1 alone (13 months vs. 11 months).[10] Moreover, in the recent international phase III trial (FLAGS), S-1 plus cisplatin had lower toxicity but achieved equally overall survival compared with 5-FU plus cisplatin (CF) (Ajani JA, et al. presented at the 2009 Gastrointestinal Cancers Symposium). Triplet chemotherapy of CF plus epirubicin (ECF) or CF plus docetaxel (DCF) is effective but more toxic than CF.[11]

However, the influence of preoperative chemotherapy on D2 or D3 surgery has not been fully evaluated, although D2 and D3 gastrectomy are safe procedures in Japan.[12] Unlike D0 or D1 surgery, D2 or D3 gastrectomy involves nodal dissection along the pancreas, which can cause pancreatic fistula or abdominal abscess. These complications can be lethal and might be increased by preoperative chemotherapy. The effect of preoperative chemotherapy on surgical mortality or morbidity with these procedures has not been fully clarified. Recently, preoperative chemotherapy of CPT-11 plus cisplatin followed by D3 dissection was tested in phase II trial to evaluate the efficacy and toxicity in Japan.[13] However, this trial has been terminated due to high treatment-related death during the accrual. A safe and effective regimen before extended surgery has yet to be reported.

The Japan Clinical Cancer Research Organization (JACCRO) therefore, conducted a multi-institutional phase II trial (JACCRO GC-01) to evaluate the feasibility and safety of preoperative chemotherapy with S-1 plus cisplatin followed by curative D2 or D3 gastrectomy for clinically serosa-positive (T3–4) gastric cancer.

Patients and methods

Eligibility criteria

Eligibility criteria were: (1) histologically proven gastric adenocarcinoma; (2) stage clinically assessed as T3–4 N0–N3 which is classified according to 2nd English Edition of Japanese Classification of Gastric Carcinoma,[1] and M0; (3) age 20–75 years; (4) Eastern cooperative oncology group (ECOG) performance status 0–1; (5) no prior therapy; (6) sufficient organ function [white blood cell count (WBC) 4000–12,000 mm^3, platelet count (PLT) >100,000/mm^3, glutamic oxaloacetic transaminase (GOT) <80 IU/l, glutamic pyruvic transaminase (GPT) <80 IU/l, total bilirubin <1.5 mg/dl, alkaline phosphatase (ALP) < two times greater than upper limit of normal, creatinine <1.2 mg/dl, creatinine clearance >60 ml/min, and hemoglobin >8.0 g/dl]; and (7) written informed consent. Clinical diagnosis was based on gastric fiberscopy, upper gastrointestinal series, computed tomography, and ultrasonography. Serosal invasion of the primary tumor was evaluated by computed tomography. Endoscopic ultrasonography or diagnostic laparoscopy was not mandatory, because these remain outside of routine preoperative examinations in Japan. Exclusion criteria were (1) severe co-morbidities; (2) active and acute bleeding from the digestive tract; (3) insufficient oral intake; (4) synchronous or previous malignancy other than carcinoma *in situ*; and (5) contraindications to S-1 or cisplatin. All patients provided informed consent before registration and were registered centrally at the JACCRO Data Center by means of the online Flexible licence assisted data server (FLADS) system. The JACCRO Data Center conducted the data management, central monitoring, and statistical analysis.

Preoperative chemotherapy

On the basis of previous reports S-1 (80 mg/m^2) was given orally every day for 3 weeks and cisplatin (60 mg/m^2) was administered intravenously on day 8 as one course.[9,10] If the patient had a WBC of 2000/mm^3 or lower, neutrophil count of 1000/mm^3 or lower, PLT of 75,000/mm^3 or lower, diarrhea or mucositis of grade 3 or higher, GOT or GPT of grade 2, or serum creatinine of grade 1, chemotherapy was postponed until recovery from these adverse events and the next dose of S-1 was reduced to 70 mg/mm^2. For diarrhea or mucositis of grade 1, chemotherapy was postponed until recovery. In the case of GOT and/or GPT of grade 3 or higher or serum creatinine of grade 2 or higher, chemotherapy was terminated. If the patient had cardiac or neurologic toxicities, chemotherapy was postponed until recovery from these toxic effects and confirmation of their cause. For any other adverse events of grade 2 or higher, chemotherapy was postponed until recovery. If the chemotherapy was postponed but the toxicities had not resolved within 21 days, the chemotherapy was terminated after this period.

Surgery

Tumor resectability was assessed after completion of chemotherapy. Resection criteria were (1) R0 resection was anticipated by D2 or extended D2 gastrectomy; (2) sufficient organ function (WBC $>3000/mm^3$, neutrophils $>1000/mm^3$, PLT $>100{,}000/mm^3$, GOT <100 IU/l, GPT <100 IU/l, creatinine <1.5 mg/dl); and (3) no active infection. Patients who fulfilled these criteria were treated by D2 or D3 gastrectomy with curative intent between two and four weeks after finishing chemotherapy. The precise procedure of D2 and D3 dissection has been reported previously.[12,15] Combined resections of adjacent organs were permitted when these procedures were indispensable for curative resection.

Treatment defined by the protocol

The treatment protocol was defined as completed when a patient received preoperative chemotherapy and underwent R0 resection by gastrectomy with D2 or D3 dissection. The treatment protocol was stopped when: (1) response was evaluated as progressive disease during chemotherapy; (2) the patient did not meet the criteria for surgery after chemotherapy; (3) the patient underwent surgery after chemotherapy but this took the form of exploratory laparotomy, bypass, or non-R0 resection; (4) the patient refused further participation; or (5) the doctor recommended stopping the protocol. After the treatment protocol was stopped, any treatment was allowed and postoperative adjuvant therapy was not defined.

Endpoints

Primary endpoint was toxicities. Secondary endpoints included response rate and overall survival.

Evaluation

The response rate was evaluated only in patients with measurable lesions; Response Evaluation Criteria in Solid Tumors (RECIST) criteria were used[16] and response to chemotherapy was evaluated by external review committee. Adverse reactions during chemotherapy were evaluated by National Cancer Institute – Common Toxicity Criteria Version 2.0.[17]

Statistical hypothesis

As it is difficult to predict the occurrence of severe adverse events or treatment-related deaths and to calculate sample size, feasibility and safety was evaluated in calculated sample size based on the response rate to be required in this setting. A Simon optimal two-stage design[18] was used to calculate the sample size, assuming an anticipated response rate of 50% and a threshold response rate of 30% with 10% alpha error and 10% beta error. Using this design, if at least 8 objective responses were observed among 22 patients in the first stage, an additional 24 patients would be recruited to the second stage. Taking into account tumors without measurable lesions and patients not fulfilling the eligibility criteria, sample size was determined to be 50. Statistical analysis was performed with SAS version 9.1 (SAS Institute, Cary, NC). This phase II trial was approved by the JACCRO Protocol Review Committee and the institutional review board of each of the 8 JACCRO institutions involved.

Results

Patients

Between February 2004 and January 2005, 50 patients were enrolled and the study was terminated. During the accrual, unpredicted severe adverse events or treatment-related death was not observed. One of these patients declined to participate, while the other 49 were eligible and received the treatment protocol. Table 1 shows patient demographics and tumor characteristics. Clinically apparent nodal disease was observed in 40 patients.

Preoperative chemotherapy and toxicities

Of all 49 eligible patients, 3 did not receive cisplatin because of S-1-related toxicity. The average proportion of actual dose to proposed dose was 94% (2219.2 mg/2348.6 mg) for S-1 and 94% for cisplatin (87.8 mg/

Table 1
Patient demographics and pre-treatment tumor characteristics (all eligible patients, $n = 49$).

Age (median, range)	62, 20–73
Sex (male/female)	36/13
PS (0/1)	46/3
Macroscopic type	
1	4
2	6
3	24
4	14
5	1
Histologic type	
Differentiated	17
Undifferentiated	31
Miscellaneous	1
Depth of tumor invasion	
T3	44
T4	5
Nodal status[a]	
N0	9
N1+, perigastric	17
N2+, along major branch arteries	12
N3+, para-aortic	11

[a] Nodal status was classified according to 2nd English Edition of Japanese Classification of Gastric Carcinoma.[14]

92.0 mg). Adverse events during chemotherapy are shown in Table 2. There were no grade 4 and a few grade 3 toxicities.

Clinical response

Clinical response could be evaluated in 34 patients who had enlarged lymph nodes as target lesions as defined by RECIST criteria. There were 13 responders (all showed partial response); 18 patients had stable disease and 3 had progressive disease. Thus, 13 of 34 evaluable patients demonstrated a clinical response (38%) with a 95% confidence interval from 22% to 56%.

Surgery

All of the 49 patients who completed chemotherapy underwent surgery. Surgical findings are shown in Table 3. Three patients underwent exploratory laparotomy due to massive peritoneal dissemination, and 7 underwent palliative D0 or D1 resection due to peritoneal dissemination or extended lymph node metastasis. Curative resection was intended for the remaining 39 patients; D2 was performed in 27 and D3 in 12. Thus, D2 or D3 was performed in 39 of all eligible 49 patients. Consequently, R0 resection was performed in 38 patients, R1 in 1 due to positive peritoneal cytology, and R2 in 7 due to peritoneal dissemination or extended lymph node metastases (Table 3). Thus, the proportion of R0 resections was 78% (38 of all eligible 49 patients), with a 95 per cent confidence interval from 66% to 89%.

Surgical morbidity and mortality

Surgical complications are shown in Table 4. There was no operative mortality. On the other hand, operative morbidity was observed in 5 of the 49 patients including pancreatic fistula in 1 and abdominal abscess in 2. No anastomotic leakage was observed and no patients required re-operation for morbidity.

Table 2
Adverse events during chemotherapy in all eligible patients ($n = 49$).

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Leukocytes	48	0	1	0	0
Neutrophils	38	4	5	2	0
Hemoglobin	40	7	2	0	0
Platelets	48	0	1	0	0
Total bilirubin	48	1	0	0	0
GOT	46	2	1	0	0
GPT	47	1	1	0	0
ALP	46	3	0	0	0
BUN	45	0	4	0	0
Urine creatinine	47	1	1	0	0
Urine protein	47	1	1	0	0
Anorexia	33	8	5	3	0
Nausea	37	6	4	2	0
Vomiting	42	3	4	0	0
Diarrhea	45	3	1	0	0
Pigmentation	45	3	1	0	0

Table 3
Surgical findings in all operated patients ($n = 49$).

Type of surgery	
Proximal gastrectomy	1
Distal gastrectomy	18
Total gastrectomy	27
Exploratory laparotomy	3
Dissection ($n = 46$)[a]	
D0	4
D1	3
D2	27
D3	12
Combined resection	
Spleen	13
Pancreas	4
Gall bladder	8
Spleen + pancreas	2
None	22
Operation time (minutes)	
Median, range	232, 25–590
Blood loss (ml)	
Median, range	342, 0–2760

[a] Three missing cases were exploratory laparotomy.

Pathological response

Details of pathological data are shown in Table 5. A total of 18 patients were diagnosed as pathological T1 or T2 disease. The pathological response rate in resected patients, defined by the degeneration/necrosis area $\geq 1/3$, was 39%. On the other hand, nodal status, which was classified by 2nd English Edition of Japanese Classification of Gastric Carcinoma, was evaluated in 39 patients who underwent D2 or D3 gastrectomy. Pathological N0 was observed in 8 patients.

Overall survival

Survival time was estimated in all 49 patients who were eligible. Median follow-up period was 31 months from 27 to 38 months. The overall survival curve is shown in Fig. 1. The three-year survival rate was 43.0% with a 95% confidence interval from 35.6% to 50.3%.

Discussion

This multi-institutional phase II prospective trial demonstrated neither treatment-related death nor severe adverse

Table 4
Surgical complications in all operated patients ($n = 49$).

	Number of patients	%
Anastomotic leakage	0	0
Pancreatic fistula	1	2
Abdominal abscess	2	4
Pneumonia	0	0
Ileus	0	0
Wound infection	1	2
Renal dysfunction	1	2

Table 5
Pathological results.

Depth of tumor invasion ($n = 46$[a])	
T1	3
T2	15
T3	19
T4	9

Nodal status[b] ($n = 39$[c])			
	D2	D3	D2/D3
N0	7	1	8
N1	12	3	15
N2	6	4	10
N3	2[d]	4	6

[a] Three missing cases were exploratory laparotomy.
[b] Nodal status was classified according to 2nd English Edition of Japanese Classification of Gastric Carcinoma.[14]
[c] Ten missing cases included exploratory laparotomy in 3, palliative D0 in 4 and palliative D1 gastrectomy in 3.
[d] Two cases were determined by a few lymph nodes of N3 dissected in addition to D2 dissection.

events by preoperative chemotherapy of S-1 plus cisplatin followed by extended surgery, suggesting that this multimodality treatment was safe and feasible.

Surgical mortality

No operative mortality was observed in the study, although 39 of the 49 patients underwent D2 or D3 surgery after preoperative chemotherapy. In the Japan Clinical Oncology Group (JCOG) 9501 phase III trial that compared D2 and D3 resections, mortality rate was reported to be 0.8% in both arms.[12] Thus, our results suggested that mortality of D2 or D3 was not increased by preoperative chemotherapy with S-1 plus cisplatin. In the retrospective study evaluating the feasibility and safety of preoperative chemotherapy of S-1 plus cisplatin followed by D2 dissection, no operative mortality was reported.[20,21] In the MAGIC phase III trial comparing surgery alone versus pre- and postoperative chemotherapy combined with surgery for resectable gastric cancer, operative mortality was 5.6% in the chemotherapy group and 5.9% in the surgery group, suggesting that mortality did not increase by preoperative chemotherapy (with an ECF regimen).[19] However, in that trial, most patients underwent less than D2 surgery. On the other hand, in JCOG 0001 trial evaluating the efficacy and safety of preoperative chemotherapy of CPT-11 plus cisplatin followed by D3 surgery, operative mortality was observed in 2.0%.[13] Thus, operative mortality may depend on the toxicity of the preoperative chemotherapy and the extent of the lymph node dissection.

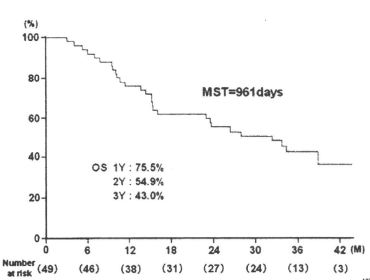

Figure 1. Overall survival ($n = 49$). Median survival time was 31.5 months. Overall survival was 75.5% at 1 year, 54.9% at 2 years, and 43.0% at 3 years.

Pancreas-related surgical morbidity

Pancreatic fistula is the major specific complication after D2 or greater extended surgery. In this study, pancreatic fistula was observed in 1 patient and abdominal abscess in 2 patients. As no apparent anastomotic leak was found in the latter 2 patients, the abdominal abscess might have been caused by pancreatic fistula. Thus, pancreatic fistula might have been a complication in a maximum of 3 of 49 patients in the present study, a proportion almost equivalent to that found in the JCOG 9501 phase III trial.[12] In that trial, tumors were diagnosed as T2–T4, N0–N2, and P0 by surgical findings.[12] In the present study, on the other hand, all tumors were clinically diagnosed as T3–T4. Moreover, 11 of the present patients had clinically apparent N3 disease. Hence, although the tumors were more advanced in this study, the rate of pancreatic fistula was not increased by preoperative chemotherapy with S-1 plus cisplatin. On the other hand, pancreatic fistula was observed in 12.2% in JCOG 0001 trial consisting of CPT-11 plus cisplatin followed by D3 dissection.[13] Toxic regimen could increase the rate of pancreatic fistula.

Overall surgical morbidity

In the present study, overall surgical morbidity was 5 of 49 which was slightly lower than the 20.9% to 28.1% observed in the JCOG 9501 trial.[12] In particular, anastomotic leakage and re-operation were not observed in this study, while rates of these events were 1.9% and 2.7%, respectively, in the JCOG 9501 study.[12] Thus, operative morbidity did not increase with the present preoperative chemotherapy regimen. In the MAGIC trial, morbidity was similar in both arms of the trial; 45.3% in the surgery alone group and 45.7% in chemotherapy group.[19] Because our preoperative chemotherapy was performed only short term, operative morbidity appears not to increase even after D2 or D3 surgery.

Chemotherapy-related toxicities

Chemotherapy-related toxicities were relatively mild in this study. There were no grade 4 toxicities and only a few grade 3 toxicities including neutropenia, anorexia, and nausea. In the SPIRITS trial,[10] grade 3/4 bone marrow suppression was more frequently observed when compared with the present trial. Chemotherapy was limited to one course in this study while it continued until disease

progression in the SPIRITS trial, which would explain the difference in the toxic profile between the two studies. Our results may also suggest that mild toxicities led to high compliance with this chemotherapy regimen and low morbidity and mortality of D2 or D3 resection.

Response to the chemotherapy

The present study achieved a relatively high response rate of 38%, which was almost the same as observed in the pathological response of the primary tumor. Previous trials in metastatic gastric cancer have demonstrated that response rate was 76% in a phase II trial[9] and 54% in the SPIRITS phase III trial.[10] The response rate in this study was slightly lower, which may be attributable to only one course of chemotherapy being administered in the present study. In the MAGIC phase III trial, three courses of ECF chemotherapy were performed preoperatively.[19] Considering the low toxicities of one course of S-1 plus cisplatin and the low mortality and morbidity of subsequent extended surgery, an additional two or three courses of this chemotherapy should be evaluated in another phase II study.

Survival

In the present study, all patients were clinically diagnosed with T3 or T4 disease before entry and overall 3-year survival rate was 43.0%. It has been reported that clinical diagnosis of T3–T4 was accurate in 74.4% in clinical T3 tumors and 87.0% in clinical T4 tumors.[5] M0 was evaluated by computed tomography and diagnostic laparoscopy was not mandatory in this study, therefore, peritoneal metastases may not be excluded in this series.[22] Retrospective analyses of Cancer Institute Hospital of Japan have reported 5-year survival rates of 25.3% and 1.8% in pathological T3 and T4 with any N, respectively.[5] In this series of patients, the 3-year survival rate was 43% despite that R0 resection was only performed in 77.6%. Although it may be difficult to compare these survival rates, our results appear to be worthy of further investigation using the same strategy.

Conclusion

In conclusion, preoperative chemotherapy with one course of S-1 plus cisplatin followed by gastrectomy with D2 or D3 dissection seems to be feasible and safe for clinically serosa-positive (T3–4) gastric cancer.

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Conflict of interest

No authors have any conflict of interest.

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特集 ····· Stage Ⅳ胃癌における外科治療の有用性 ·····

腹腔洗浄細胞診陽性例に対する肉眼的治癒切除の意義

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Significance of R1 Resection in Patients with Positive Peritoneal Cytology: Terashima M*1, Bando E*1, Tokunaga M*1, Tanizawa Y*1, Kawamura T*1, Kondo J*1, Sugisawa N*1, Taki Y*1, Ohsima N*1, Motegi Y*1, Miki Y*1, Yamakawa Y*1, Makuuchi M*1, Kinugasa Y*2, Kanemoto H*2, Uesaka K*2, Yasui H*3 and Boku N*4 (*1Division of Gastric Surgery, *2Division of Gastrointestinal Surgery, *3Division of Medical Oncology, Shizuoka Cancer Center, *4Department of Internal Medicine, St. Marianna University, School of Medicine Hospital)

Positive peritoneal cytology (CY1) is regarded as M1 disease and classified into stage Ⅳ. However, it is still controversial whether the prognosis in patients with CY1 is same as hepatic metastasis or peritoneal seeding or not. In order to determine the optimal treatment strategy for patients with CY1, we retrospectively evaluated the results of patients with CY1. A total of 123 patients with M1(CY1) without other non-curative factors and underwent gastrectomy were included in this study. There was a significant difference of survival betweenR1 and R2 resection. In the multivariate analysis in patients underwent R1 resection, N-factor, D2 lymph node dissection, and adjuvant chemotherapy with S-1 were selected as independent prognostic factor. The median survival time and 5-year survival rate in patients underwent R1 resection with D2 lymphadenectomy and adjuvant S-1 treatment were 42 months and 46%, respectively. In patients with positive peritoneal cytology without other non-curative factors, D2 lymph node dissection to achieve R1 resection and adjuvant chemotherapy using S-1 is recommended.

Key words: Gastric cancer, Peritoneal cytology, D2 lymph node dissection, R1 resection, Adjuvant chemotherapy
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はじめに

以前からわが国においては腹腔洗浄細胞診に関する研究が広く行われており，腹腔洗浄細胞診陽性例はきわめて予後が不良であることが報告されてきた[1,2]．これらの研究結果を受けて1999年に発行された胃癌取扱い規約第13版から腹腔細胞診（CY）が規定され，細胞診陽性（CY1）はすなわちStage Ⅳであり，肉眼的な根治切除が行われても根治度Cに分類される事になった[3]．最近改訂されたTNM分類第7版においても洗浄細胞診によるステージングが導入され，細胞診陽性は肝転移や腹膜転移と同様に遠隔転移（M1）に分類され，residual tumorにおいても肉眼的な根治切除が行われたとしてもR1（microscopic

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residual tumor）に分類される[4]．今回改訂された胃癌取扱い規約第14版[5]でも同様の分類が採用されている．しかし，CY1が他の遠隔転移と同様の予後を示すか否かについては疑問であり，特にわが国においてはS-1の開発以降[6,7] CY1であっても術後のS-1投与により長期生存する症例もしばしば経験する．これまで当施設においても他に非治癒因子の無いCY1症例に対しては可能な限り肉眼的治癒切除（R1）を行い，術後S-1を投与してきた．

そこで，今回CY1単独によるStage Ⅳ症例に対する至適な治療戦略を検索する目的で，これまでのR1切除症例の治療成績について検討した．

1 対象と方法

2002年10月から2009年6月までに当科で加療を行った胃癌2,299例中，他に非治癒因子が無く腹腔洗浄細胞診にてCY1と診断され，切除が施行された123例を対象とした．

これらの症例において，臨床病理学的因子，生存期間並びに多変量解析による予後因子の解析について検討した．

臨床病理学的因子に関しては胃癌取り扱い規約第13版に準じて記載したが，腫瘍の遺残（R）のみは同第14版[5]に準じた．

生存曲線はKaplan-Meier法にて作成し，生存期間の解析にはCoxの比例ハザードモデルを用いた．

2 結　果

1 CY1切除症例の臨床病理学的因子

CY1切除症例の臨床病理学的因子の検討（表1）では，一般の胃癌と比較して，女性の割合が比較的高く，当然の事ながらT3以深の症例が大多数を占めていた．93%の症例でリンパ節転移を伴っており，肉眼的には3型，4型の症例が3/4を占めており，組織学的には約2/3の症例が未分化型であった．

実際に行われた治療内容（表2）では，癌の進行度を反映してか胃全摘の症例が59%を占め，膵頭十二指腸切除も4例に施行されていた．リンパ節郭清に関しては，D2以上の郭清が実施された症例が約半数を占める一方，残りの半数の症例ではD1+αやβに留まっていた．その結果，根治度に関しては85%の症例でR1切除が可能であった．

表1　CY1切除症例の背景因子

年齢	65.8±10.6	組織型	
性別		分化型	33
男性	78	未分化型	90
女性	45	肉眼型	
胃壁深達度		0	2
T1	1	1	4
T2	22	2	23
T3	88	3	65
T4	12	4	28
リンパ節転移程度		5	1
N0	9	腹腔洗浄細胞診	
N1	35	Class Ⅳ	11
N2	63	Class Ⅴ	112
N3	16		

表2　CY1切除症例に実施された治療内容

切除術式	幽門側胃切除	46
	胃全摘	73
	膵頭十二指腸切除	4
郭清程度	D1+α	32
	D1+β	23
	D2	66
	D3	1
根治度（TNM）	R1	105
	R2	18
術後S-1投与	あり	95
	なし	28

2 CY1症例における根治度別の生存期間の検討

CY1症例における生存転帰の解析では，治癒切除の程度で最も大きな差が認められた（図1）．R1切除例の生存期間中央値（MST）は20.5月であったのに対し，R2切除例では11.0月と著明に短縮しており有意な差が認められた．R因子が最も重要な予後因子であり，R2切除例は少数例のみであったため以降予後因子の解析はR1切除

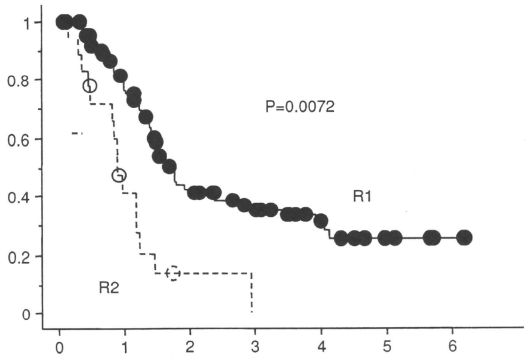

図1　CY1切除症例における根治度別の生存曲線

例に限って検討した．

3）CY1, R1切除例における生存期間の検討

表3にCY1でかつR1切除が可能であった症例における臨床病理学的因子と生存期間との関連について単変量解析，多変量解析の結果を示した．単変量解析の結果では，壁深達度，リンパ節転移程度では有意な差が認められず，リンパ節郭清程度（<D2 vs ≧D2），術後S-1投与の有無のみで有意な差が認められた（表3）．

一方，多変量解析の結果では，リンパ節転移程度，リンパ節郭清程度，術後S-1投与が有意な独立した予後因子として選択された．

4）CY1, R1切除，>D2郭清，術後S-1投与症例の生存曲線

上記の解析の結果で良好な予後を示すと思われる，>D2郭清が施行され，術後S-1が投与された症例の生存曲線に関して検討した（図2）．D2以上の郭清が施行されてかつ術後S-1が投与された症例のMSTは42月で，5年生存率は46%であった．

表3　CY1, R1切除例における臨床病理学的因子と生存期間との関連

臨床病理学的因子	単変量解析		多変量解析	
	HR	p値	HR	p値
性別				
男性	1.000		1.000	
女性	0.906	0.7094	0.956	0.8726
壁深達度				
T1, T2	1.000		1.000	
T3, T4	1.471	0.2043	1.783	0.0877
リンパ節転移				
N0, N1	1.000		1.000	
N2, N3	1.324	0.2938	1.919	0.0264
組織型				
分化型	1.000		1.000	
未分化型	1.063	0.8260	1.027	0.9283
リンパ節郭清程度				
D1, D1+α, D1+β	1.000		1.000	
D2, D3	0.572	0.0308	0.476	0.0059
術後S-1投与				
なし	1.000		1.000	
あり	0.498	0.0154	0.430	0.0102

3．考　察

これまでCY1症例はきわめて予後が不良であり，腹膜播種を有する症例と同程度の生存期間を示すと認識されてきた[1,2]．そのため，胃癌取り扱い規約においても第13版以降は，CY1すなわちStage Ⅳであり，仮に肉眼的に根治切除がなされても根治度Cに分類される事になった．したがって胃癌治療ガイドラインにおいても，化学療法，放射線治療，緩和手術，対症療法が日常診療として推奨されており，これはつい最近改訂さ

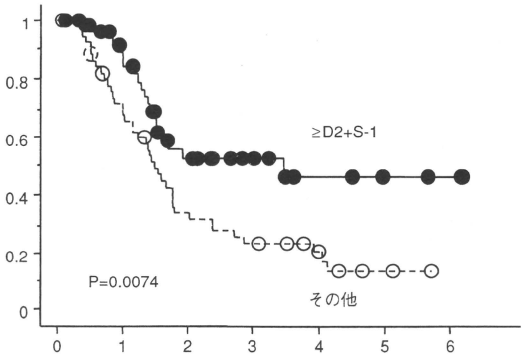

図2　CY1, R1 切除例中≥ D2 郭清，術後 S-1 投与症例の生存曲線

れた第3版でも同様の扱いである[8]．

しかし，その後わが国において開発された S-1 が胃癌に対して優れた抗腫瘍効果を示す事が確認され，進行再発胃癌[6]のみならず，Stage Ⅱ，Ⅲ の根治切除例に対する補助化学療法においても有効性が証明されるようになった[7]．CY1 症例に対して至適な補助療法は確立されていなかったため，当院では S-1 単独による化学療法（原則として1年間）が施行されていた．

CY1 切除例の背景因子の解析では，これまで報告されてきた結果[1,2]と同様に，肉眼型が3型，4型の進行胃癌で，未分化型で漿膜浸潤陽性の腫瘍が大半を占めていた．

これらの症例における予後因子の解析では，リンパ節転移の程度とともに，リンパ節郭清程度，根治度，術後 S-1 投与が予後因子として選択された．つまり，CY1 は Stage Ⅳ であり肉眼的治癒切除を行っても根治切除にはならないとは言え，その予後は他の遠隔転移を有する症例とは明らかに異なっており，可能な限り腫瘍遺残量の少ない手術を施行する事が重要と思われた．また，術後 S-1 を投与する事により有意に生存期間の延長が認められる事から，Stage Ⅱ，Ⅲ の根治切除例と同様，CY1 症例においても術後 S-1 投与の有効性が示唆された結果である．寺本ら[9]は CY1 の予後予測性に関して検討し，他に非治癒因子の無い CY1 症例は，他の Stage Ⅳ と同様に扱うべきではないと結論している．また，岩下ら[10]は CY1 症例の予後因子に関して検討し，P0CY1 の症例では D2 以上の郭清により R1 切除を目指し，術後化学療法を行う事により良好な予後が得られる可能性を示唆している．いずれも今回のわれわれの検討結果を支持するものである．

もちろん，今回の検討は retrospective な解析であるため，様々な bias が生じていることは否めない．CY1 と言っても全身状態が比較的良好で，腫瘍量が少ない症例に限って D2 以上の郭清がなされ，術後の S-1 投与が実施されていた可能性も否定できない．CY1 症例に対して至適な治療戦略が確立されていない現状では，curative intent で開腹手術に望んだ場合には可及的に肉眼的根治切除を目指して，その後 S-1 による化学療法を施行する事が推奨される．しかし，この治療法が最善であるという根拠は無い．中川ら[11]は CY1 症例に対して術前化学療法を施行する事により 78％の症例で CY の陰性化が得られる事を報告している．術前診断で CY1 の高危険群に対しては審査腹腔鏡を施行し，CY1 であれば術前化学療法を施行する事により治療成績の向上が得られる可能性もある．また，CY1 症例は抗癌剤の腹腔内投与の良い適応である事も示唆されている[12]．このように CY1 単独で Stage Ⅳ に分類される症例に対しては，様々な治療法により治療

成績の向上が得られる可能性が残されている．今後，前向きの臨床試験により至適な治療戦略の確立が切望される．

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Influence of a Positive Proximal Margin on Oral Intake in Patients with Palliative Gastrectomy for Far Advanced Gastric Cancer

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Abstract
Background Resection margin involvement is one of the most significant risk factors for local recurrence in curative gastrectomy, and local recurrence results in anastomotic stenosis. In the present study, the effects of a positive resection margin in palliative gastrectomy on the symptoms of anastomotic stenosis and the amount of oral intake were analyzed.
Methods Between September 2002 and December 2009, 2,228 patients underwent resection for gastric cancer at Shizuoka Cancer Center, Japan, of whom 18 underwent palliative gastrectomy with a positive proximal margin because of urgent symptoms such as tumor bleeding, stenosis, or perforation. These 18 patients were analyzed retrospectively in this study.
Results Twelve patients had a positive proximal margin, and six patients had both proximal and distal margin involvement. Anastomotic leakage occurred in 2 patients. The median overall survival was 7.5 months, and the median time from operation to a decrease in oral intake was 5.5 months. Anastomotic recurrence developed in 3 patients, and in all of them, anastomotic stricture was found 2–3 months after gastrectomy. One of these patients, who was in good general condition, was treated by endoscopic balloon dilatation. The other 2 patients did not undergo balloon dilatation because their general condition was poor, with peritonitis carcinomatosa.
Conclusions It does not appear necessary for palliative gastrectomy to achieve a negative proximal margin, because salvage therapies resulted in maintaining a tolerable oral intake in patients who were in good general condition.

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Introduction

Gastric cancer is a very common disease worldwide and the second most frequent cause of cancer death, affecting about one million people per year [1]. Surgery is the only curative therapy for advanced gastric cancer, and this involves removing the primary lesion with an adequate tumor-free margin [2, 3]. However, the prognosis of advanced gastric cancer patients with noncurable factors, such as hepatic or peritoneal metastasis, is extremely poor [4]. The role of noncurative gastrectomy in patients with far advanced gastric cancer remains unclear. The rationale for offering palliative gastrectomy to patients with far advanced gastric cancer is that the primary tumor will result in gastric obstruction, perforation, or tumor bleeding [5, 6]. Several studies have suggested that the morbidity after palliative gastrectomy for far advanced gastric cancer that needs urgent treatment may be higher [7–10]. Patients who undergo palliative gastrectomy have only a short time to live, so postoperative morbidity is directly related to the quality of the rest of their life. On the other hand, patients who require palliative gastrectomy are those with advanced locoregional disease, so patients with severe tumor invasion into the esophagus from the stomach are not unusual [11–13]. It is difficult and risky to achieve a negative proximal margin in gastric cancer with wide spread into the esophagus, because a highly placed anastomosis in a narrow working space is required. Resection margin

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involvement is one of the most significant risk factors for local recurrence in curative gastrectomy, and local recurrence results in anastomotic stenosis [14, 15]. However, in palliative gastrectomy, a positive resection margin might not be a risk factor for anastomotic recurrence, because patients who undergo palliative gastrectomy usually succumb to metastatic disease before anastomotic recurrence develops. One of the outcomes of palliative gastrectomy is the prolongation of oral intake, but anastomotic stenosis caused by local recurrence might prevent oral intake. Some reports have shown that a positive resection margin has no predictive value for survival in patients with late-stage gastric cancer [16, 17]. However, the effects of a positive resection margin in palliative gastrectomy on the symptoms of anastomotic stenosis and the amount of oral intake are unknown. In the present study, the clinical course, focusing mainly on the amount of oral intake, of patients who underwent palliative gastrectomy with a positive proximal margin was analyzed.

Materials and methods

Between September 2002 and December 2009, 2,228 patients underwent resection for gastric cancer at Shizuoka Cancer Center, Japan. A positive proximal margin was found on final pathological analysis of the resected specimen in 20 patients who underwent palliative gastrectomy. In all of them, the status of the proximal margin was negative on macroscopic examination. Of the 20 patients, 2 were lost to follow-up. Therefore, 18 patients with urgent symptoms, such as tumor bleeding, stenosis, or perforation, were analyzed retrospectively in this study. All 18 patients were routinely followed at Shizuoka Cancer Center at least once a month postoperatively, and the patients were asked detailed questions about the amount of oral intake and the presence of symptoms of anastomotic stenosis. Endoscopic examination was not performed routinely; it was performed only when the patients complained of obstructive symptoms. We investigated the time between the operation and the decrease in oral intake. The time to decrease in oral intake was defined as the time when total parenteral nutrition or tube feeding was required. The data collected included patient demographics, clinicopathologic features, and clinical course. To compare this study population with patients who underwent palliative gastrectomy with a negative proximal margin, the data of 46 patients who underwent palliative gastrectomy with a negative proximal cut end were collected. Stage was reported according to the Seventh Edition of the tumor-node-metastasis (TNM) classification of malignant tumor established by the International Union Against Cancer (UICC) classification [18].

Results

The patients ranged in age from 49 to 85 years, with a median age of 70 years. Overall, 8 patients were male, and 10 patients were female. The patient characteristics are shown in Table 1. Twelve patients had a positive proximal margin, and 6 patients had both proximal and distal margin involvement. The symptoms leading to palliative gastrectomy were gastric outlet obstruction and/or tumor bleeding. Ten patients suffered from gastric outlet obstruction, 3 patients had severe anemia caused by tumor bleeding, and 5 patients had both. No patients underwent palliative gastrectomy for tumor perforation. Noncurable factors included liver metastasis in 4 cases, lymph node metastasis in 9 cases, peritoneal metastasis in 14 cases, and positive peritoneal cytology in 18 cases. Operative data are shown in Table 2. Total gastrectomy was performed in 14 patients, distal gastrectomy was performed in 3, and 1 patient underwent proximal gastrectomy. Systematic lymph node dissection was not performed in any of the patients. All patients underwent D1 lymphadenectomy, 14 underwent R2 resection, and 4 underwent R1 resection. Postoperative complications occurred in 5 patients.

Anastomotic leakage occurred in 2 patients: 1 patient in an esophagojejunostomy with tumor involvement after total gastrectomy, and 1 patient in a duodenal stump that

Table 1 Patient characteristics ($n = 18$)

Characteristic	
Age, years, median (range)	70 (49–85)
Sex	
Male	8 (44%)
Female	10 (56%)
Symptoms	
GOO	10 (56%)
Tumor bleeding	3 (17%)
GOO and tumor bleeding	5 (28%)
Noncurable factors	
Peritoneal lavage cytology	
Positive	18 (100%)
Negative	0
Peritoneal metastasis	
Positive	14 (78%)
Negative	4 (22%)
Liver metastasis	
Positive	4 (22%)
Negative	14 (78%)
Distant lymph node metastasis	
Positive	9 (50%)
Negative	9 (50%)

GOO gastric outlet obstruction