the resolution of MDCT,[8] differentiated type tumors, from which elevated type tumors often derive, tended to be over-staged compared with undifferentiated ones. Further examination of a larger number of cases is necessary to confirm these findings.

In early gastric cancer, the limitation of MDCT in differentiating submucosal cancers from mucosal ones[27] suggests that MDCT will not be helpful in selecting patients for laparoscopic surgery or endoscopic resection. In contrast, considering the close concordance with the status of peritoneal disease and prognosis, T-staging by MDCT seemed useful clinically, because MDCT might provide data that contribute to treatment strategies such as preoperative chemotherapy in advanced gastric cancer. When diagnosed as a T1 or T2-3 tumor with no distant metastases by MDCT, patients might undergo curative resection without any preoperative therapies, but when diagnosed as T4a or deeper, patients might be considered for staging laparoscopy to recognize peritoneal disease. For T4a tumors with peritoneal dissemination or positive cytology, or for T4b tumors determined by MDCT, patients might require chemotherapy for down-staging or to improve survival. In such a setting, MDCT might also be useful for evaluating the response to these neoadjuvant treatments by determining T-stage before and after preoperative therapies.[38] We hope that our findings will offer important information and contribute to treatment strategies for patients with advanced gastric cancer.

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Phase II Feasibility Study of Adjuvant S-1 plus Docetaxel for Stage III Gastric Cancer Patients after Curative D2 Gastrectomy

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Key Words

Gastric cancer · Adjuvant chemotherapy · S-1 · Docetaxel · Gastrectomy · D2 lymph node dissection

Abstract

Objective: The aim of this prospective study was to evaluate the feasibility and safety of adjuvant S-1 plus docetaxel in patients with stage III gastric cancer. ***Methods:*** We enrolled 53 patients with pathological stage III gastric cancer who underwent D2 gastrectomy. They received oral S-1 (80 mg/m^2/day) administration for 2 consecutive weeks and intravenous docetaxel (40 mg/m^2) on day 1, repeated every 3 weeks (1 cycle). The treatment was started within 45 days after surgery and repeated for 4 cycles, followed by S-1 monotherapy (4 weeks on, 2 weeks off) until 1 year after surgery. The feasibility of the 4 cycles of chemotherapy, followed by S-1 administration, was evaluated. ***Results:*** A total of 42 patients (79.2%, 95% CI 65.9–82.9) tolerated the planned 4 cycles of treatment with S-1 and docetaxel, and 34 patients (64.2%, 95% CI 49.8–76.9) completed subsequent S-1 monotherapy for 1 year. Grade 4 neutropenia was observed in 28% and grade 3 febrile neutropenia in 9% of the patients, while grade 3 nonhematological toxicities were relatively low. ***Conclusions:*** Adjuvant S-1 plus docetaxel therapy is feasible and has only moderate toxicity in stage III gastric cancer patients. We believe that this regimen will be a candidate for future phase III trials seeking the optimal adjuvant chemotherapy for stage III gastric cancer patients.

Introduction

The principal aims of adjuvant chemotherapy for curatively resected gastric cancer are to prevent distant or local recurrence and improve the survival of patients. In Japan, several studies concerning postoperative adjuvant chemotherapy for patients with gastric cancer have been performed since 1960, but none of these studies demonstrated therapeutic benefits of adjuvant chemotherapy [1–6].

The National Surgical Adjuvant Study Group for Gastric Cancer study evaluated postoperative chemotherapy for patients with T2, N1–2 gastric cancer from 1998 using uracil-tegafur (an oral fluoropyrimidine prodrug) for 18 months, excluding stage I gastric cancer, based on an analysis of previous studies. Although this study was interrupted because of the introduction of S-1 and the start

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of a new large-scale trial – the Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC) – using S-1 for stage II and III gastric cancer from 2001, the results of this study showed that adjuvant chemotherapy with uracil-tegafur was effective for T2, N1–2 gastric cancer [7].

In an ACTS-GC study, adjuvant chemotherapy using S-1 has been reported to be effective for Japanese stage II and III gastric cancer patients who have undergone a D2 dissection. This trial was stopped on the recommendation of the independent data and safety monitoring committee, because the first interim analysis, performed 1 year after completion of enrollment, showed that the 3-year overall survival (OS) rate of 80.1% in the S-1 group was higher than that of 70.1% in the surgery-only group. However, in stage III gastric cancer patients, the difference in the 3-year OS rate between the S-1 group and the surgery-alone group was less than that in stage II [8].

Therefore, to improve the prognosis for patients with advanced gastric cancer after curative resection, more effective chemotherapy is required for patients with stage III gastric cancer.

Recently, several combination chemotherapeutic regimens involving S-1 and other anticancer drugs such as cisplatin, taxanes and irinotecan (CPT-11) have been reported to yield and increased overall response rates and prolonged median survival time [9–12].

In these studies, in patients with advanced gastric cancer, S-1 plus docetaxel has shown that the response rate and median OS was 56% and 14.3 months, respectively. Moreover, gastrointestinal toxicities of this combination regimen were reported to be comparatively few and low grade: anorexia (6.3%), stomatitis (10.4%) and nausea (6.3%), which was considered to be advantageous for the postoperative patients [10].

Therefore, S-1 plus docetaxel may be a promising regimen for stage III advanced gastric cancer after curative resection, as well as being a candidate for an experimental arm in the next adjuvant chemotherapy trial.

The aim of this phase II study was to evaluate the feasibility and safety of adjuvant chemotherapy of S-1 plus docetaxel for stage III gastric cancer patients.

Patients and Methods

Eligibity Criteria

The eligibility criteria of this study were: (1) histologically proven gastric cancer of stage IIIA or IIIB after R0 surgery with D2 lymph node dissection; (2) age 20–80 years; (3) Eastern Cooperative Oncology Group performance status 0–1; (4) no previous treatment for cancer except for the initial gastric resection for the primary lesion; (5) adequate digestive function; (6) duration of the period from surgery <6 weeks, and (7) adequate organ function, including a leukocyte count between 4,000 and 12,000 mm^3, a neutrophil count >2,000 mm^3, a platelet count >100,000 mm^3, a hemoglobin count >9.0 g/dl, aspartate aminotranferase and alanine aminotransferase levels within 2.5 times the upper limit of the normal range, a serum bilirubin level <1.5 mg/dl, a serum creatinine level <1.2 mg/dl, and creatinine clearance of at least 60 ml/min. Moreover, absence of other severe medical conditions and an absence of synchronous or metachronous malignancy were needed for this study.

Exclusion criteria were as follows: infection or suspected infection with fever; congestive heart failure; uncontrolled diabetes or hypertension; interstitial pneumonia or lung fibrosis; symptomatic brain metastasis; liver cirrhosis or active hepatitis, and pregnancy. Patients with a history of prior chemotherapy were also excluded.

Written informed consent was obtained from each patient before enrollment and the protocol was approved by the institutional ethics committees of the participation centers.

The eligibility criteria for stage classification was judged in accordance with the guidelines of the Japanese Gastric Cancer Association [13] and all patients were additionally staged using the 6th edition of UICC TNM staging system [14].

Study Design

In this feasibility study, oral S-1 (80 mg/m^2/day) was administered for 2 consecutive weeks and intravenous docetaxel (40 mg/m^2) on day 1, repeated every 3 weeks (1 cycle). The treatment was started within 45 days after surgery and repeated for 4 cycles. After 4 cycles of this treatment, S-1 was administered as daily monotherapy according to the schedule of the ACTS-GC study until 1 year after surgery. Namely, patients received 2 oral doses of 40 mg/m^2 of S-1 per day, for 4 weeks, followed by 2 weeks of no chemotherapy. If patients had hematological toxic effects of grade 3 or 4 or nonhematoligic toxic effects of grade >2, their dose of docetaxel was reduced from 40 to 35 mg/m^2, and at the same time, the dose of S-1 was reduced from 120 to 100 mg, or from 100 to 80 mg or from 80 to 50 mg per day.

The primary endpoint was the feasibility of completing 4 cycles of S-1 plus docetaxel; the secondary endpoints were safety, disease-free survival, OS and feasibility of S-1 administration until 1 year after surgery. The definition of feasibility of administration was 'treatment completion rate >75% at 4 cycles of S-1 plus docetaxel therapy' and the completion of treatment rate was defined as follows: (full analysis set – number of discontinued patients by adverse events)/number of all patients × 100.

We adopted the combination chemotherapy method reported by Yoshida et al. [10], using the same schedule. Although it is difficult to decide how many cycles of S-1 plus docetaxel should be performed in an adjuvant setting, we decided to carry out this study with 4 cycles of S-1 plus docetaxel based on the results of a study using an average of 4 courses reported by Yoshida et al. [10], which was performed for patients with advanced and recurrent gastric cancer.

Follow-Up

Patients underwent hematologic tests and assessments of clinical symptoms at least once during every course of chemotherapy. The presence of a relapse was determined by means of imaging

Table 1. Patient characteristics

		Patients (n = 53)
Age, years	Median	65
	Range	43–78
Gender	Male	42
	Female	11
ECOG PS	0	31
	1	22
Pathological type	Intestinal	23
	Diffuse	29
	Others	1
Stage[1]	IIIA	36
	IIIB	17
T stage[2]	pT2	21
	pT3	30
	pT4	2
N stage[2]	pN0	1
	pN1	22
	pN2	30
M stage[2]	M0	53
	M1	0
Stage[2]	IIIA	36
	IIIB	16
	IV (T4, N1)	1

ECOG PS = Eastern Cooperative Oncology Group performance status.
[1] Japanese classification. [2] TNM classification.

studies, including ultrasonograpy, computed tomography and gastrointestinal endoscopy. Patients underwent abdominal computed tomography at 6-month intervals during the first 2 years after surgery, at 1-year intervals thereafter until 5 years after surgery, and also underwent gastrointestinal endoscopy at 1-year intervals.

Statistical Analysis

The calculation of the sample size for the study was based on an expected feasibility rate of 75% and a threshold feasibility rate of 50%, using a 2-sided α error of 0.05 and a statistical power of 90%. The planned sample size was 50 patients, allowing for a 20% dropout rate. The feasibility rate was evaluated by exact binomial test. Statistical analysis was done using R software version 2.12.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient Characteristics

We enrolled 53 patients from 13 institutions for this study, 42 men and 11 women with a median age of 65 years (range 43–78), between May 2007 and August 2008.

Table 2. Adverse events of 4 cycles of chemotherapy with S-1 plus docetaxel (n = 53)

	G1	G2	G3	G4	≥G3, %
Hematologic					
Anemia	20	11	2	0	3.3
Leukopenia	7	17	7	3	18.9
Neutropenia	4	4	11	15	49.1
Thrombocytopenia	7	0	0	0	3.8
Febrile neutropenia	–	–	5	0	9.4
Nonhematologic					
AST/ALT	7	0	0	0	0
Total bilirubin	4	3	0	0	0
Nausea	9	3	3	0	5.7
Vomiting	2	2	0	0	0
Anorexia	16	7	5	0	9.4
Fatigue	12	8	3	0	5.7
Stomatitis	5	1	1	0	1.9
Diarrhea	6	3	0	0	0
Alopecia	5	3	–	–	0

National Cancer Institute Common Toxicity Criteria, version 3.0. AST = Aspartate aminotransferase; ALT = alanine aminoransferase.

Thirty-six patients had stage IIIA disease and 17 patients had stage IIIB disease. The demographic and clinicopathological characteristics of these patients are listed in table 1.

Toxicity

The most frequent grade 3–4 hematological toxicity during 4 cycles of this regimen was neutropenia, which was observed in 26 of 53 patients (49.1%) (table 2). Grade 3 febrile neutropenia was observed in 5 patients (9%). Additional grade 3–4 hematological toxicities consisted of leukopenia in 10 patients (18.9%) and anemia in 2 patients (3.8%). Nonhematological toxicities of grade ≥3 involved nausea in 5.7%, anorexia in 9.4% and fatigue in 5.7%. There was no grade 4 nonhematological toxicity in any patient.

No treatment-related deaths occurred within 30 days after completion of this regimen.

Feasibility

The feasibility of the planned 4 cycles of treatment was 79.2% (95% CI 65.9–89.2; $p < 0.001$ under the null hypothesis) with 42 out of 53 patients (table 3). Reasons for discontinuation of this regimen were adverse events in 9 patients, by physician's decision in 1 patient, and 1 patient postponed the treatment schedule due to personal rea-

Table 3. Feasibility of protocol treatment

	S-1 plus docetaxel for 4 cycles	S-1 plus docetaxel and S-1 monotherapy for 1 year
Patients	53	53
Completed	42	34
Not completed	11	19
Treatment completing rate	79.2% (65.9–89.2)	64.2% (49.8–76.9)

Figures in parentheses are 95% CIs.

sons. A total of 42 patients completed 4 cycles of S-1 and docetaxel, but 8 patients did not follow the planned S-1 monotherapy: 3 due to recurrent cancer, 2 due to toxicity, 1 due to patient refusal, 1 due to the physician's decision, and 1 due to personal reasons.

The relative performance of S-1 and docetaxel for 4 cycles of chemotherapy was 79.6 and 87.8%, respectively. Moreover, the compliance rates of S-1 patients were 84.9, 73.6, 69.8 and 64.2% (95% CI 49.8–76.95) at 3, 6, 9 and 12 months after surgery, respectively.

Discussion

This phase II study demonstrated that postoperative adjuvant S-1 plus docetaxel therapy of 4 cycles is feasible, with a feasibility rate of 79.2%. Moreover, the compliance of S-1 treatment was similar to those of the ACTS-GC study up to 1 year after surgery: 84.9 versus 87.4% at 3 months, 73.6 versus 77.9% at 6 months, 69.8 versus 70.8% at 9 months and 64.2 versus 65.8% at 12 months, respectively [8].

Since there were few gastrointestinal toxicities during an additional 4 courses of docetaxel, this combination regimen seemed to be highly tolerable. These results may have important implications for future adjuvant treatment strategies for stage III gastric cancer.

In Japan, for metastatic or recurrent gastric cancer, S-1 plus cisplatin is now considered to be one of the standard regimens based on a phase III trial (SPIRITS study) [16].

The results of the SPIRITS study (S-1 vs. S-1 plus cisplatin) established the superiority of the S-1 plus cisplatin combination over S-1 monotherapy [15]. The rate of response to combination therapy versus monotherapy was 54 versus 31% ($p = 0.0018$), and the median survival time was 13.0 versus 11.0 months ($p = 0.0366$).

Therefore, S-1 plus cisplatin is considered to be a candidate for an experimental arm in the next adjuvant chemotherapy trial.

More recently, adjuvant chemotherapy studies using S-1 plus cisplatin have been reported for patients with resected gastric cancer [16, 17]. Five courses of S-1 plus cisplatin appear to be too toxic as postgastrectomy treatment for clinical stage II/III patients who underwent gastrectomy but turned out to be stage IV gastric cancer, so that the median relative dose intensities of S-1 and cisplatin were only 37 and 40%, respectively [16]. Moreover, a feasibility study of adjuvant chemotherapy with 3 courses of S-1 plus cisplatin followed by S-1 monotherapy until 1 year after surgery demonstrated that 3 courses of combined chemotherapy were not feasible because of the high incidence of grade 3–4 toxicities including neutropenia (40%), anorexia (28%) and nausea (8%) [17]. In this clinical trial, they suggested the modified protocol, the first chemotherapy cycle of which consisted of S-1 monotherapy; then, cisplatin was added to cycles 2, 3 and 4, followed by S-1 monotherapy up to 1 year after surgery. This amended protocol is more feasible than the original protocol, because of relatively few grade 3–4 toxicities including neutropenia (37%), anorexia (8%) and nausea (3%) and should be considered as a feasible experimental arm for the next postoperative adjuvant phase III trial [17].

Nausea and anorexia are commonly observed adverse reactions after the administration of cisplatin, and dehydration due to impaired oral food intake could increase the renal toxicity of cisplatin, especially in patients immediately after gastrectomy.

On the other hand, preclinical pharmacokinetic studies on docetaxel have shown that its hepatobiliary excretion is the major route of elimination, while renal excretion is minimal (<5%) [18–20]. Thus, it seems that docetaxel is a suitable anticancer agent for patients immediately after surgery. Moreover, S-1 plus docetaxel can be given in outpatient clinics, while S-1 plus cisplatin usually requires hospitalization to ensure hydration; thus, the former reduces the inconvenience to both patients and clinicians.

In both Japan and Korea, phase III studies of S-1 alone versus S-1 and docetaxel (JACCRO GC03 study) as chemotherapy for advanced gastric cancer are ongoing and the results should be reported soon [21].

If the results of the JACCRO GC03 study are favorable, it seems that the present regimen will become a promising candidate for adjuvant chemotherapy in stage III gastric cancer.

In conclusion, postoperative adjuvant chemotherapy with S-1 and docetaxel of 4 cycles and S-1 monotherapy afterwards until 1 year after surgery is considered to be feasible for patients who have undergone gastrectomy for gastric cancer.

This should be regarded as a potential experimental arm together with S-1 plus cisplatin for the next adjuvant phase III study comparing S-1 plus other drug combination chemotherapy and S-1 alone as adjuvant chemotherapy for patients who have undergone curative resection with D2 lymph node dissection for stage III gastric cancer.

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Phase II trial of preoperative S-1 plus cisplatin followed by surgery for initially unresectable locally advanced gastric cancer

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Abstract

Background: The aim of this study was to evaluate the efficacy and feasibility of preoperative chemotherapy with S-1 plus cisplatin in patients with initially unresectable locally advanced gastric cancer.
Methods: We enrolled patients with initially unresectable locally advanced gastric cancer because of severe lymph node metastases or invasion of adjacent structures. Preoperative chemotherapy consisted of S-1 at 80 mg/m^2 divided in two daily doses for 21 days and cisplatin at 60 mg/m^2 intravenously on day 8, repeated every 35 days. If a tumor decreased in size, patients received 1 or 2 more courses. Surgery involved radical resection with D2 lymphadenectomy.
Results: Between December 2000 and December 2007, 27 patients were enrolled on the study. No CR was obtained, but PR was seen in 17 cases, and the response rate was 63.0%. Thirteen patients (48.1%) had R0 resections. There were no treatment related deaths. The median overall survival time (MST) and the 3-year overall survival (OS) of all patients were 31.4 months and 31.0%, respectively. Among the 13 patients who underwent curative resection, the median disease-free survival (DFS) and the 3-year DFS were 17.4 months and 23.1%, respectively. The MST and the 3-year OS were 50.1 months and 53.8%, respectively. The most common site of initial recurrence after the R0 resection was the para-aortic lymph nodes.
Conclusions: Preoperative S-1 plus cisplatin can be safely delivered to patients undergoing radical gastrectomy. This regimen is promising as neoadjuvant chemotherapy for resectable gastric cancer. For initially unresectable locally advanced gastric cancer, new trials using more effective regimens along with extended lymph node dissection are necessary.

Keywords: Neoadjuvant chemotherapy; Lymph node dissection; Bulky lymph node; TS-1; Cisplatin; Para-aortic lymph node

Introduction

Gastric cancer is still one of the most common cancers in the world; 876,000 new cases were anticipated worldwide in the year 2000.[1] In Japan, 110,323 new cases were anticipated in the year 2003 and the 5-year survival rate of gastric cancer diagnosed from 1993 to 1996 was 54.4%.[2,3]

Currently, surgery remains the mainstay of curative treatment. However, only an R0 resection is associated with significant cure rates. Patients having microscopic (R1) or macroscopic (R2) residual tumor have an extremely poor prognosis.[4]

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Preoperative and neoadjuvant chemotherapy represent investigational options. The rationale of preoperative chemotherapy is based on the difficulty of performing an R0 resection in patients with initially unresectable locally advanced tumors and the high risk of micrometastatic disease in these patients. Neoadjuvant chemotherapy has potential for resectable gastric cancer for the purpose of treating micrometastases.

Intensive chemotherapy is necessary for the improvement of the R0 resection rate and complete elimination of the micrometastases. However, it is difficult for patients who undergo gastrectomy to tolerate intensive chemotherapy. Because weight decreases by gastrectomy, it is necessary to reduce the dose of chemotherapy. The tolerance to chemotherapeutic agents with digestive organ toxicity was often reduced by gastrectomy-related gastrointestinal effects.

S-1 (TS-1, Taiho Pharmaceutical, Tokyo, Japan) is an orally active combination of tegafur (a prodrug that is converted by cells to fluorouracil), gimeracil (an inhibitor of dihydropyrimidine dehydrogenase, which degrades fluorouracil), and oteracil (which inhibits the phosphorylation of fluorouracil in the gastrointestinal tract, thereby reducing the gastrointestinal toxic effects of fluorouracil) at a molar ratio of 1:0.4:1. The response rate of S-1 alone exceeded 40% in two phase 2 trials involving patients with metastatic gastric cancer.[5,6] The combination chemotherapy of S-1 plus cisplatin (CDDP) achieved a high response rate (74%, 95%CI: 54.9–90.6) in a previous phase I/II study of patients with metastatic gastric cancer.[7]

These factors led us to perform the current phase II trial to investigate the use of an active preoperative chemotherapy regimen. The primary objectives of the trial were to investigate tolerance to the preoperative regimen, its effects on operative morbidity and mortality, and the response rate. Secondary objectives included evaluation of the R0 resection rate, disease-free and overall survival, and failure pattern.

Patients and methods

Patients

The study was conducted as a prospective multi-institutional phase II trial by the Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG) in Japan. All patients had histologically confirmed adenocarcinoma of the stomach. They also had to have initially unresectable locally advanced tumors because of invasion to adjacent structures or severe lymph node metastases, staged by contrast-enhanced CT as T2-3N2-3M0 or T4NanyM0, according to the Japanese Classification of Gastric Carcinoma (2nd English Edition).[8] They also had to have lymph node metastases that were measurable according to the RECIST[1.0] guidelines.[9] We did not require laparoscopic staging as an entry criterion for this study. Any sites of suspected M1 disease had to be ruled out prior to entrance into the study. No prior chemotherapy or radiation was allowed. The age range was 20–75 years. The performance status (ECOG) was 0 from 1.

Because of the worse prognosis of type IV gastric cancer, also known as scirrhous or linitis plastica, we excluded such cases.[10] Acceptable hematologic profile (WBC $\geqq$ 4000 cells/mm^3, hemoglobin $\geqq$ 8.0 g/dl, platelets $\geqq$ 100,000 cells/mm^3), and renal (BUN $\leqq$ 25 mg/dl, creatinine $\leqq$ 1.2 mg/dl and/or creatinine clearance $>$ 60 ml/min) and hepatic function (total serum bilirubin $<$ 1.5 mg/dl) were required. In addition, certain respiratory function test results (ratio of the forced expiratory volume in one second $\geqq$ 50%, PaO2 in room air $\geqq$ 70 mmHg) were required criteria. No clinically significant auditory impairment was allowed. Patients with prior cancer diagnosed during the previous 5-year period (except for colon carcinoma *in situ*) were excluded. Other exclusion criteria included significant cardiac disease, pregnancy or serious infections. The protocol was reviewed and approved by the Institutional Review Board of each institution. All patients gave written informed consent.

Preoperative chemotherapy

Patients found to have locally advanced gastric cancer as defined above, received two cycles of S-1 plus cisplatin every 35 days. Preoperative chemotherapy consisted of S-1 at 80 mg/m^2 divided in two daily doses for 21 days and cisplatin at 60 mg/m^2 intravenously on day 8. Physical examination, abdominal CT scan and assessment of toxicity were performed prior to each cycle. The response measurement of the preoperative chemotherapy was carried out according to the RECIST[1.0] guidelines. Because it was preoperative chemotherapy, response was not confirmed at least 4 weeks apart. Toxicity was recorded and graded according to the National Cancer Institution Common Toxicity Criteria (NCI-CTC) version 2.0 scale. Operative complication was graded according to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE v4.0). If a tumor decreased in size, according to protocol criteria, we added 1 or 2 more courses. If curative resection was considered possible after planned chemotherapy, the patient had surgery. If curative resection was considered difficult, a further course of chemotherapy was added. The doses of both agents were attenuated for grade $\geqq$3 toxicities, using standard reduction criteria.

Surgery

The surgery was planned for 3–6 weeks from the day of last administration of chemotherapy. Surgery involved a radical resection, the extent of which (total or distal gastrectomy) depended on the site of the primary tumor, with a D2 lymphadenectomy. We performed D2 or more dissection in patients with metastasis to N3 lymph nodes before chemotherapy. Spleen preservation in total gastrectomy procedure was entrusted to the decision of each clinician.

Patients in whom curative resection was impossible underwent palliative operation. The postoperative treatment was left to the decision of each physician.

Biostatistical considerations

The 3 primary end points of the study were as follows; 1) tolerance to preoperative chemotherapy, 2) operative morbidity and mortality, and 3) objective response rate (ORR). Secondary end points were R0 resection rate, failure pattern, and disease-free and overall survival. One of the primary end points was ORR. The number of patients to be enrolled was calculated at 24, which was required given the assumption that the 95% confidence interval (CI) would be ±20%, assuming an expected response rate of 60%. Finally, we set the number as 30 patients in consideration of disqualified patients. The early stopping criterion of the trial was 3 treatment related deaths. Analogous samples were used to estimate the response rate, R0 resection rate, operative morbidity and mortality, and incidence of treatment related grade 3–4 toxicity. Overall survival (OS) of all patients was calculated from the day of registration in the trial. OS and disease-free survival (DFS) of the patients who underwent R0 resections were calculated from the day of surgery. Survival distributions were estimated using the Kaplan–Meier method.

Follow-up

Following completion of chemotherapy and surgery, patients were followed at 3- monthly intervals until year 3. Thereafter, 6-month follow-up visits were performed. CT scans and appropriate blood studies were performed on the occasion of each evaluation.

Results

Patient population

Between December 2000 and December 2007, 27 patients with initially unresectable local advanced gastric cancer were enrolled into the study from 9 institutions. As shown in Table 1, the male to female ratio was 20:7. The median age was 63 years. As for the histologic type, 15 cases were undifferentiated (including signet ring cell carcinoma) and 11 cases were differentiated type. One case was classified as mucinous carcinoma. There were 3 cStage IIIa (11.1%) preoperatively, 8 cStage IIIb (29.6%), and 16 cStage IV (59.3%).

Preoperative chemotherapy

The median number of preoperative chemotherapy regimens was 3 courses. Grade 3–4 toxicities associated with preoperative S-1/CDDP are described in Table 2. Hematologic toxicity (Grade 3/4) was 7.4% and non-hematologic toxicity (Grade 3/4) was 3.7%. Treatment was generally well tolerated and no chemotherapy-related deaths were observed. While there was no CR, there were 17 cases of PR and the response rate was 63.0% [95%CI: 42.4–80.6] (Table 2).

Table 1
Patient characteristics ($n = 27$).

		Number	%
Age, years	Median (range)	63	(48–75)
Gender	Male	20	74.1
	Female	7	25.9
Histology	Differentiated	11	40.7
	Undifferentiated	15	55.6
	Other	1	3.7
Pretreatment cStage	T2N2M0 (IIIA)	3	11.1
	T3N2M0 (IIIB)	7	25.9
	T4N1M0 (IIIB)	1	3.7
	T2N3M0 (IV)	5	18.5
	T3N3M0 (IV)	6	22.2
	T4N2M0 (IV)	3	11.1
	T4N3M0 (IV)	2	7.4

Operative outcome

All patients who were entered into this trial had initially unresectable tumors. Nine patients were diagnosed as being unresectable when chemotherapy was completed and did not undergo surgery. Eighteen patients (66.7%) underwent laparotomy (Table 3). Thirteen patients (48.1%) had R0 resections. Three patients (11.1%) underwent R1 surgery, because of positive results of peritoneal washing cytology. Two patients underwent simple laparotomy because of peritoneal metastases or unresectable local extension of metastatic lymph nodes. Postoperative complications are described in Table 3. The incidence of complications was 22.2%. One patient underwent operative intervention because of pancreatic leakage; however, there were no surgery-related deaths.

Table 2
Courses, responses and toxicities of preoperative chemotherapy.

				n	%
Courses	Median (range)			3	(1–9)
Response	CR			0	0.0
	PR			17	63.0
	SD			6	22.2
	PD			4	14.8
Toxicities		Grade1/2		Grade3/4	
		n	%	*n*	%
	Neutropenia	10	37.0	2	7.4
	Thrombocytopenia	3	11.1	1	3.7
	Hemoglobin	21	77.8	1	3.7
	Vomiting	7	25.9	1	3.7
	Nausea	13	48.1	1	3.7
	Diarrhea	4	14.8	1	3.7
	Anorexia	17	63.0	1	3.7
	Cerebral infarction	0	0	1	3.7
Treatment related death				0	0.0

Table 3
Operative outcome ($n = 27$).

		Number	%
No operation		9	33.3
Operation		18	66.7
	R0 resection	13	48.1
	R1 resection	3	11.1
	R2 resection	0	0
	Simple Laparotomy	2	22.2
Complications			
	None	14	77.8
	Pancreatic leak	3 (Grade 1: 2, Grade 4: 1)	16.7
	Lymphorrhea	1 (Grade 1)	5.6
	Anastomotic leak	0	0.0
Re-operation		1	5.6
Mortality		0	0.0

Seven of 9 patients who did not undergo surgery received 2nd-line chemotherapy (S-1: 3 patients, S-1/CPT-11: 2 patients, CPT-11/CDDP: 1 patient, Paclitaxel: 1 patient). Four of 5 patients who underwent R1-2 surgery received further chemotherapy (S-1/Paclitaxel: 2 patients, S-1: 1 patient, CPT-11/CDDP: 1 patient).

Overall survival of all patients

Only one patient was lost to follow-up at 8 months from the first day of preoperative chemotherapy, but all other patients were followed more than three years. The median overall survival time and the 3-year overall survival rate of all patients were 31.4 months and 31.0% [95%CI: 17.5–55.1], respectively.

DFS, OS, and first relapse site of patients who underwent R0 resection

Thirteen patients underwent R0 resection. The details of these patients are shown in Table 4. Twelve of these 13 patients (92.3%) achieved PR after preoperative chemotherapy. The median number of course of chemotherapy of these patients was 3 (2–5). Of these patients, only 2 patients (15.4%) underwent D2 plus para-aortic lymph node dissection (D3). Downstaging was observed in 11 patients (84.6%). Seven of 13 patients received postoperative adjuvant chemotherapy (S-1: 4 patients, S-1 plus CDDP: 1 patient, CPT-11: 1 patient, CPT-11/CDDP: 1 patient). To date, recurrence has been diagnosed in 10 patients. First relapse site of five of ten patients was para-aortic lymph nodes. The median disease-free survival time and the 3-year disease-free survival rate of the 13 patients were 17.4 months and 23.1% [95%CI: 8.6–62.3], respectively (Fig. 1A). The median overall survival time and the 3-year overall survival rate of the 13 patients were 50.1 months and 53.8% [95% CI: 32.6–89.1], respectively (Fig. 1B).

Discussion

The combination chemotherapy of S-1 plus cisplatin was chosen because it had achieved a high response rate of 74% (95%CI: 54.9–90.6) in previous phase I/II study of patients with metastatic gastric cancer. The incidences of severe (Grade 3/4) hematological and non-hematological toxicities were 15.8 and 26.3%, respectively.[7] A randomized controlled trial in Japan showed the superiority of S-1/cisplatin compared with S-1 monotherapy according to the response rate and survival for metastatic gastric cancer.[11] Therefore, S-1/cisplatin therapy is now the standard treatment for metastatic gastric cancer in Japan.

This multi-institutional phase II prospective trial of preoperative chemotherapy in initially unresectable locally advanced gastric cancer showed that preoperative chemotherapy using S-1/cisplatin was not only feasible but also achieved a high response rate. The overall response rate was 63.0% [95%CI: 42.4–80.6]. The incidence of grade 3/4 toxicities was less than 10% and treatment related

Table 4
Patients who underwent R0 resection.

No.	cStage	Course	Response	Gastrectomy	D	Combined resection	fStage	Nodes	First relapse
1	T3N2M0 (IIIB)	2	PR	Distal	D3	Liver, Gallbladder	T2N2M0 (IIIA)	4	None
2	T3N3M0 (IV)	3	PR	Total	D2	Spleen, Panc. (tail) Gallbladder	T2N2M0 (IIIA)	6	Brain
3	T3N2M0 (IIIB)	2	PR	Total	D2	Spleen	T2N2M0 (IIIA)	10	Lymph (para AO)
4	T3N2M0 (IIIB)	2	PR	Distal	D3	None	T2N2M0 (IIIA)	3	None
5	T3N2M0 (IIIB)	3	PR	Total	D1*	Liver	T2N0M0 (IB)	0	None
6	T2N2M0 (IIIA)	2	SD	Distal	D2	Panc. (head)	T4N3M0 (IV)	7	Peritoneum
7	T4N2M0 (IV)	3	PR	Total	D2	Spleen, Panc. (tail)	T3N2M0 (IIIB)	10	Lymph (para AO)
8	T2N3M0 (IV)	4	PR	Distal	D2	Gallbladder	T2N2M0 (IIIA)	1	Bone
9	T4N3M0 (IV)	3	PR	Distal	D2	None	T1N0M0 (IA)	0	Lung
10	T4N1M0 (IIIB)	3	PR	Total	D2	Spleen	T2N2M0 (IIIA)	4	Lymph (hepatic)
11	T2N3M0 (IV)	5	PR	Total	D1*	None	T2N3M0 (IV)	2	Lymph (para AO)
12	T2N2M0 (IIIA)	3	PR	Total	D1*	None	T2N0M0 (IB)	0	Lymph (para AO)
13	T3N2M0 (IIIB)	3	PR	Total	D1*	None	T2N2M0 (IIIA)	13	Lymph (para AO)

D1*: we performed almost D2 dissection, but it classified D1 dissection according to the Japanese classification of gastric carcinoma (2nd English edition), because of preserving spleen.

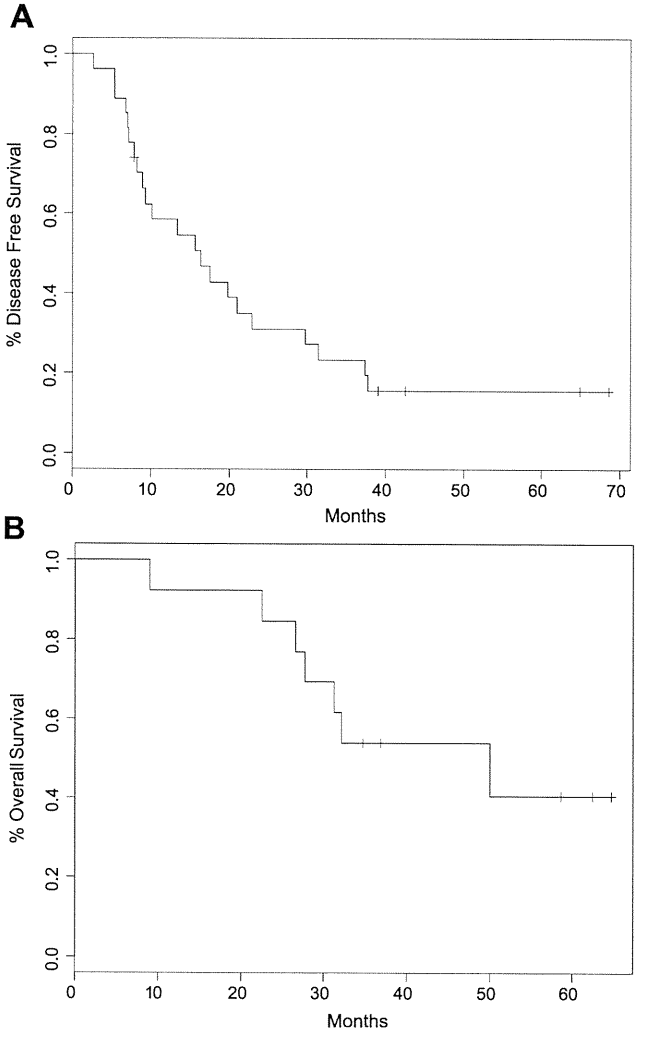

Figure 1. Disease-free and overall survival of the patients who underwent R0 surgery ($n = 13$).

mortality was 0.0%. Similar results were reported in other studies.[12,13] These results encourage the use of S-1/cisplatin combination chemotherapy as neoadjuvant treatment for patients who have resectable gastric cancer. Such trials are currently under way in Japan.[14,15]

The recently completed MAGIC trial constitutes a larger study regarding neoadjuvant chemotherapy in gastric cancer. In this study, 503 patients were randomized to three cycles of pre- and three cycles of postoperative epirubicin/cisplatin/5-FU (ECF) chemotherapy or surgery alone. Neoadjuvant chemotherapy was tolerable and was completed in 88% of patients. Significant downsizing (5.0 versus 3.1 cm median tumor size, $P < 0.001$), downstaging (54% versus 36% T1–T2 tumors, $P = 0.01$) and enhanced resectability (79% versus 69%, $P = 0.02$) were noted. Improved progression-free survival and survival were demonstrated, with an overall 5-year survival of 36% versus 23% for those undergoing surgery alone.[16] We should conduct phase III clinical trials of the neoadjuvant chemotherapy of S-1/cisplatin therapy for resectable gastric cancer.

In Japan, the ACTS-GC trail demonstrated a survival advantage of postoperative adjuvant chemotherapy after R0 resection. R0 patients were randomized to adjuvant chemotherapy using S-1 (529 patients) versus surgery alone (530 patients); improved survival (3-year overall survival rates of 80.1% versus 70.1%, $P = 0.003$) was noted.[17] Adjuvant chemotherapy, as reported by the ACTS-GC Group, is now considered a standard treatment for R0 patients. However, of the 283 patients who had stage III disease and received S-1 adjuvant chemotherapy, 73 patients died. The hazard ratio of the adjuvant chemotherapy group worsened with an increasingly advanced stage. These results suggest that S-1 monotherapy is insufficient for patients who have stage III or more. However, for patients who have initially unresectable gastric cancer like the patients enrolled in this trial, S-1/cisplatin chemotherapy is insufficient because of the high relapse rate of patients who underwent R0 resection.

For the patients immediately after gastrectomy, highly toxic chemotherapy is difficult because of overlaps between chemotherapy-induced gastrointestinal toxicity and digestive symptoms due to gastrectomy.[18] Therefore, further improvements in preoperative therapy will require development of more effective chemotherapeutic regimens. During the last decade, several new agents with promising activity against gastric cancer were identified. These include paclitaxel, docetaxel, irinotecan and trastuzumab. These agents are now undergoing phase II and III trials, as part of combination regimens.[19–22] If improved outcome is seen in metastatic disease, these agents will undergo extensive testing in the preoperative setting.

The absence of laparoscopic staging might have allowed inclusion of patients with positive peritoneal cytology or small peritoneal implants that could have disappeared with the chemotherapy; these patients have a worse prognosis, which could have impacted on the final results. Actually, there were 3 cases of positive cytology at exploration after chemotherapy. Laparoscopic staging should be mandatorily included in future similar projects.

An interesting point is that there were many para-aortic lymph node recurrences in the patients who underwent R0 resection. Among 13 patients who underwent curative resection, initial recurrence in 5 patients was in a para-aortic lymph node. These patients had not undergone para-aortic lymph node dissection. The prognostic improvement effect of the para-aortic lymph node dissection was refuted by two clinical trials.[23,24] In the JCOG 9501 trial, 523 patients with resectable gastric cancer were enrolled, and 263 were assigned to D2 group and 260 were assigned to D2 plus para-aortic nodal dissection. The 5-year overall survival rate was 69.2% for D2 lymphadenectomy group and 70.3% for the D2 lymphadenectomy plus para-aortic nodal dissection group; the hazard ratio for death was 1.03 (95%CI, 0.77 to 1.37; $P = 0.85$). There were also no significant differences in recurrence-free

survival and the pattern of recurrence between the two groups.[23] In the East Asian Surgical Oncology Group trial, 269 patients with resectable gastric cancer were enrolled, and 135 were assigned to the D2 group and 134 were assigned to the D2 plus para-aortic nodal dissection. The 5-year overall survival rates were 52.6% for the D2 lymphadenectomy group and 55.0% for the D2 lymphadenectomy plus para-aortic nodal dissection group. There was no significant difference in survival between the two groups ($P = 0.801$).[24] It was concluded that the D2 lymphadenectomy plus para-aortic nodal dissection did not improve prognosis regarding D2 lymph node dissection in the resectable gastric cancer.

However, in these trials, patients who had gross metastases to the para-aortic nodes were excluded. The incidence of metastases in the para-aortic nodes was lower than expected in 8.5% and 9.7%, respectively. The median number of metastatic nodes was only 2 nodes among the patients who underwent D2 plus para-aortic nodal dissection in the JCOG 9501. In the East Asian Surgical Oncology Group trial, the mean number of metastatic nodes was 5.9 in the para-aortic lymph node dissection group.

Recently, 15-year follow-up results of a randomized nationwide Dutch D1D2 trial were published. 711 patients underwent randomly assigned treatment with curative intent (380 in the D1 group and 331 in the D2 group). Overall 15-year survival was 21% for the D1 group and 29% for the D2 group. Gastric cancer-related death rate was significantly higher in the D1 group (48%, 182 patients) than that in the D2 group (37%, 123 patients). Local recurrence was 22% (82 patients) in the D1 group versus 12% (40 patients) in D2, and regional recurrence was 19% (73 patients) in D1 versus 13% (43 patients) in D2. After a median follow-up of 15 years, D2 lymphadenectomy was associated with lower locoregional recurrence and gastric cancer-related death rates than D1 surgery.[25] This difference was greater in the patients with lymph node metastases from 7 to 15.[26]

The observation period was shorter in the clinical trials of JCOG and East Asian Surgical Oncology Group than in the Dutch trail, and fewer mortality events occurred and also fewer metastases to lymph nodes. Therefore, para-aortic lymph node dissection might have better prognosis in patients with severe lymph node metastases like the patients enrolled in our trial.

In summary, preoperative S-1/cisplatin can be safely delivered to patients undergoing radical gastrectomy. The response rate was high, with no increase in operative morbidity and mortality compared with those upon surgery without preoperative chemotherapy.[27] Controlled trials of neoadjuvant chemotherapy using this regimen with the postoperative S-1 monotherapy for resectable gastric cancer are necessary. For initially unresectable locally advanced gastric cancer, the rate of recurrence was high, and the most common initial recurrent site was para-aortic lymph node. New trials, using a more effective regimen along with extended lymph node dissection are necessary.

Conflict of interest statement

The authors declare no conflict of interest.

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The Roles of Surgical Oncologists in the New Era – Minimally Invasive Surgery for Early Gastric Cancer and Adjuvant Surgery for Metastatic Gastric Cancer

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Key Words
Gastric cancer · Laparoscopic surgery · Chemotherapy · Adjuvant surgery

Abstract
In the new era of technical development in surgery, operative devices, molecular targeting and chemotherapeutic agents, surgical oncologists have two main roles in the treatment of gastric cancer. One is to provide patients with minimally invasive surgery, including laparoscopy- or robot-assisted surgery in early gastric cancer patients, and the new concept of surgical intervention toward advanced and metastatic disease. Since recently, laparoscopy-assisted distal gastrectomy has become prevalent in Japan as a surgery which is minimally invasive for the patients and provides them with a good quality of life afterwards. However, the provision of advanced surgical techniques, including lymph node dissection and reconstruction, is more important for patient survival. The second role of surgical oncologists is to evaluate the significant values of the aggressive treatment which we term 'adjuvant surgery' for stage IV gastric cancer patients who have successfully responded to initial chemotherapy for curative intent. Stage IV gastric cancer patients are now being informed about the possibility of longer survival with the new chemotherapeutic and surgical strategic approach.

Introduction

Gastric cancer is the fourth most commonly diagnosed cancer and the second highest in terms of mortality rate. It is a global disease and a type of cancer frequently found in Asian countries. Recent demographic surveys have demonstrated that the mortality rate is notably decreasing, in spite of an only gradual decrease of the occurrence rate [1, 2]. The major causes of this phenomenon in Japan might be the broad reach of the general screening system of gastric cancer, and secondly, the innovation of newly developed diagnostic systems for the early detection of cancer and the high standard of operative techniques and chemotherapy [3].

According to the Japanese General Rules and Guidelines for gastric cancer [4, 5], intramucosal cancers are treated by endoscopic submucosal dissection or endoscopic mucosal resection, and minimally invasive surgery, including laparoscopic gastrectomy, is often performed for the rest of the early gastric cancers which are limited to within the submucosal layer [6–8].

The surgical treatments for stage II and III gastric cancer are well established, as demonstrated by Songun et al. [9] after a 15-year follow-up of the randomized nationwide Dutch D1D2 trial. That is to say, D2 lymphadenectomy is the recommended surgical approach for

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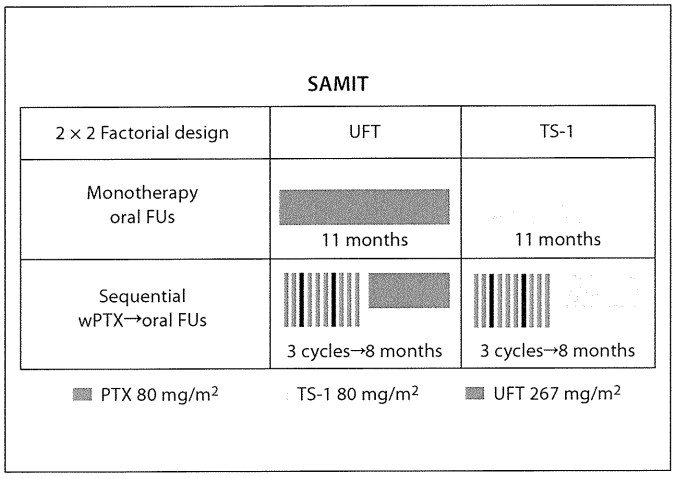

Fig. 1. The rationale of the SAMIT trial. PTX = Paclitaxel.

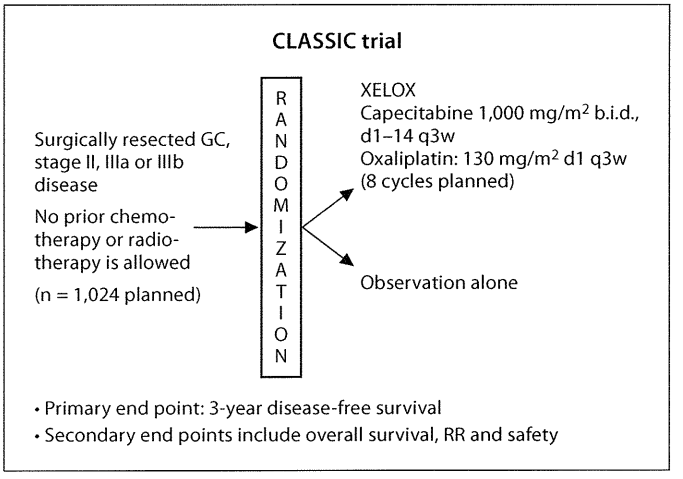

Fig. 2. The rationale of the CLASSIC trial. GC = Gastric cancer; XELOX = capecitabine in combination with oxaliplatin.

Table 1. Consensus of perioperative chemotherapy of gastric cancer

USA	SWOG 9008/Intergroup 0116 5-FU/leucovorin + radiation
Europe	MAGIC trial Perioperative ECF
Japan	ACTS-GC Postoperative S-1

patients with resectable (curable) gastric cancer, and is popular in Japan, Korea and other Asian countries. However, postoperative or perioperative treatments remain a controversial issue between the East and the West. Perioperative ECF (epirubicin/cisplatin/5-FU) therapy is regarded as the standard treatment in the UK and in some European countries [10] and intraoperative radiation with postoperative chemotherapy is the widely accepted treatment in the USA [11]. D2 lymph node dissection was not performed in most of the cases in these trials. What was interesting is that the postoperative survival of the patients who underwent D2 lymph node dissection without postoperative chemotherapy in Japan was far better than for those in the Medical Research Council Adjuvant Gastric Cancer Infusional Chemotherapy (MAGIC) trial and Intergroup study [12]. According to the results of the standard procedure of curative surgery, the Adjuvant Chemotherapy Trial of Thymidine Synthase (TS-1) for Gastric Cancer (ACTS-GC) was performed for 1 year on stage II and III patients to establish the postoperative S-1 treatment; it was accepted with significant survival benefit of the treatment group in Japan [13, 14]. The consensus of the perioperative strategies is summarized in table 1. The Stomach Cancer Adjuvant Multi-Institutional Trial (SAMIT) is currently ongoing; it compares the benefits of S-1 and UFT and also the benefits of adding paclitaxel as adjuvant chemotherapy for curatively resected patients with serosal invasion of a tumor [15]. In Korea, the CLASSIC trial is underway to establish a standard postoperative adjuvant chemotherapy with capecitabine in combination with oxaliplatin after curatively resected stage II and III gastric cancer patients have undergone D2 lymph node dissection [16] (fig. 1, 2).

There is no established global standard chemotherapy for metastatic or recurrent gastric cancer. A combination therapy of fluoropyrimidine and platinum is commonly used [17]. Data is also available about a triplet regimen. ECX (epirubicin/cisplatin/capecitabine) [18], EOX (epirubicin/oxaliplatin/capecitabine) [19] and DCF (docetaxel/cisplatin/5-FU) [20] (or modified DCF [21]) are used as standard care in certain areas of the US and the UK. S-1 combination chemotherapy (S-1 + CDDP) is currently regarded as the standard first-line treatment in metastatic gastric carcinomas in Japan [22]. The median survival time (MST) was prolonged to 13.0 months in the SPIRITS trial conducted in Japan.

As reported at ASCO 2009, a targeted therapy for HER2, Herceptin, was approved for HER2-positive gastric cancer in Europe, Korea and other areas [23]. Other targeted therapies are now under investigation in clinical

trials. Under these circumstances, we need, via clinical trials, to provide a new treatment which is more effective and has fewer adverse events throughout the world and especially in Asian countries. The data relating to gastric cancer should be obtained by collaboration between Asian countries and transmitted globally to establish a standard treatment because gastric cancer is the most prevalent and common disease in this part of the world.

What is interesting in the recent trend of chemotherapeutic treatment in stage IV gastric cancer is that downstaging of the tumors is often observed with high response rate (RR) regimens with newly developed chemotherapeutic agents, and as a result, R0 resection (complete resection with no residual microscopic tumor) has been performed on quite a few patients after chemotherapy [24, 25]. These cases can broadly be called 'adjuvant surgery' or oncosurgery (conversion therapy as it is often described in the treatment of liver metastasis in colorectal surgery) after neoadjuvant chemotherapy [26–28].

Considering the present observations described above, minimally invasive surgery, including laparoscopic surgery or robotic surgery for early gastric cancer [29], and aggressive surgery with curative intent in stage IV, or recurrent gastric cancer with perioperative chemotherapy are the main themes of surgical oncology in the new era. These points are highlighted in this article.

Minimally Invasive Surgery

Laparoscopic Surgery and Its Indication for Gastric Cancer

Laparoscopy-assisted distal gastrectomy (LADG), a minimally invasive surgery, has recently become prevalent in Japan, and provides patients with a good quality of life [30–32]. However, it is more important to provide them with advanced surgical techniques including lymph node dissection and reconstruction. According to the Japanese guidelines for gastric cancer treatment, LADG is not regarded as the standard procedure. In order to establish the safety and noninferiority of the method compared to open surgery, randomized control studies in Japan and Korea are ongoing [33, 34]. For the technical assurance of the laparoscopic surgery, a certification system has been adopted by the Japanese Society of Endoscopic Surgery.

In our institution, the indication for the operation is restricted to patients with early gastric cancer which includes: carcinomas of the mucosal layer (T1), no evidence of lymph node metastasis (N0), not suitable for endoscopic mucosal resection (with a size of more than 2 cm and with ulcer scar formation), or invaded to the submucosal layer with no clinical lymph node metastasis. Up to October 2010, we performed 204 laparoscopic gastrectomies including 152 LADG, 8 laparoscopy-assisted pylorus-preserving gastrectomies, 21 laparoscopy-assisted proximal gastrectomies, 6 laparoscopy-assisted total gastrectomies and 17 simple resections of the stomach.

Surgical Techniques

In order to perform complete laparoscopic gastrectomy, resection and anastomosis should be performed in the abdominal cavity. In this section, we describe our standard procedure of LADG and gastroduodenostomy.

We performed 103 cases of gastroduodenostomy using the delta anastomosis technique [30, 35]. Under general anesthesia, the patient was placed in the supine position with legs apart. Initially, a trocar was inserted under the umbilical portion via a 2-cm incision by the open method. Flexible laparoscopy (Olympus) was used in the operation and the camera operator stood between the legs of the patient. Four other trocars were inserted in the flank and subcostal regions.

The operation consisted of 9 parts: (1) ligation of the left gastroepiploic artery and vein [dissection of lymph node (LN) 4d and 4sb], (2) ligation of the right gastroepiploic artery and vein (LN 6), (3) transection of the duodenum, (4) ligation of the right gastric artery (LN 5), (5) dissection of LN 8a, (6) ligation of the left gastric artery and vein (LN 7, 9 and 11p), (7) dissection of LN 1 and 3, (8) transection of the stomach and (9) reconstruction by the Billroth I method with the delta anastomosis technique. The surgeon stood on the right side except during step (2) and (3).

(1) Ligation of the Left Gastroepiploic Artery and Vein (Dissection of LN 4d and 4sb)

The greater omentum was dissected with harmonic scalpel (Ethicon) about 5 cm away from the epiploic vessels; LN 4d and 4sb were removed. The left gastroepiploic artery and vein were dissected with clips.

(2) Ligation of the Right Gastroepiploic Artery and Vein (LN 6)

The surgeon stood on the left side of the patient to continue the procedure. The greater omentum of the right side was divided in the same manner towards the hepatic flexure of the colon and the gastroduodenal artery was visualized. Dissection of LN 6 was performed, with liga-

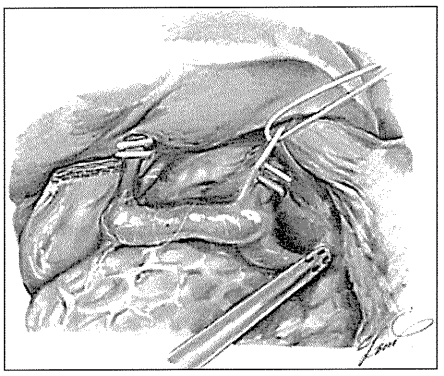

Fig. 3. Lymph node dissection by laparoscopic approach (illustrated by Leon Sakuma [30]).

tion and division of the right gastroepiploic artery and vein by harmonic scalpel.

(3) Transection of the Duodenum and (4) Ligation of the Right Gastric Artery (LN 5)

The surgeon stood on the right side of the patient again. The antrum was lifted and the duodenum was transected close to the pylorus ring using an Echelon (Ethicon) from the left lower port and then the right gastric artery was divided and dissected with the harmonic scalpel with clips cleaning the LN 5.

(5) Dissection of LN 8a

The stomach was lifted towards the left flank and the lesser omentum was divided visualizing the hepatic branch of the vagus nerve near the liver bed. Preserving the branch, the dissection was performed towards the cardia. The serosa of the right crus was dissected with the harmonic scalpel.

LN 8a was dissected using the harmonic scalpel visualizing the common hepatic artery preserving the hepatic plexus of the autonomic nerve. The dissection was performed from the right side towards the celiac axis (fig. 3).

(6) Ligation of the Left Gastric Artery and Vein (LN 7, 9 and 11p)

The fat tissue and connective tissues of LN 8a, 7, 9 and 11p were dissected with the harmonic scalpel. The left gastric artery and vein were visualized, then ligated with 2 clips and divided with the harmonic scalpel. The dissection was performed along the curus towards the esophagogastric junction.

(7) Dissection of LN 1 and 3

The dissection of the LN 1 and 3 was performed along the lesser curvature of the stomach, dissecting the anterior and posterior branch of the vagus nerves toward the stomach. The dissection was performed towards the transection line of the stomach.

(8) Transection of the Stomach and
(9) Reconstruction by the Billroth I Method with the Delta Anastomosis Technique in the Abdominal Cavity

The proximal resection margin was estimated by the serosal side carbon ink color which was injected in the submucosal layer the day before the operation by endoscopy and transected from the left lower port using Echelon (60 mm). The resected stomach was captured by the end catch and taken out through the camera port with an additional abdominal muscle fascia incision but without an additional skin incision.

For the gastroduodenostomy, the edge of greater curvature of the remnant stomach and the duodenum were opened with the harmonic scalpel and the linear stapler (endcutter 45 mm) was inserted via each hole and connected and fired. The V-shape anastomosis of gastroduodenostomy was performed with the entry hole opened. The final step was the closure of the hole with 3 firings of the linear stapler by lifting up the 3 stitches (3-0 monocryl) of incomplete closure of the entry hole (fig. 4).

The mean operative time was 253 min and blood loss was 50 ml. Thirty-seven lymph nodes were harvested. Patients started to walk the next day, started the oral intake treatment on day 3 after the operation and were discharged on day 9. Among 103 cases of delta anastomosis, there was no anastomotic leakage and no reoperation; there were, however, 2 cases of anastomotic stenosis.

Although this procedure requires time and the precise knowledge of the anatomy of the upper abdominal regions, it provides patients with several advantages including improved cosmetics, shorter hospitalization, minimal operative pains and a low incidence of bowel movability and pancreas functions (demonstrated elsewhere). Moreover, the postoperative complications can be reduced. The LADG with lymphadenectomy can be one of the most effective therapeutic methods for early gastric cancer patients.

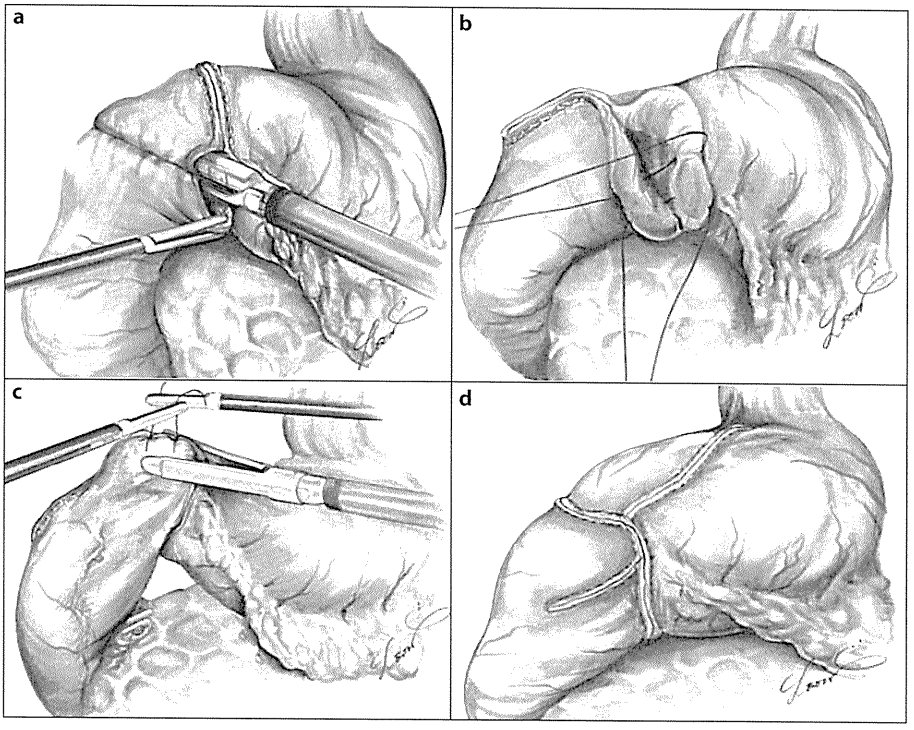

Fig. 4. Delta anastomosis (illustrated by Leon Sakuma [30]). **a** Anastomosis by linear stapler. **b** Ligation of entry hole. **c** Closure of entry hole by linear stapler. **d** Final anastomosis image.

New Therapeutic Approach for Stage IV Gastric Cancer

Establishment of New Chemotherapeutic Regimens for Gastric Cancer

Several combination regimens with S-1 have been established in Japan in this decade and randomized phase III studies have been conducted. They are S-1 + CDDP, S-1 + CPT-11 and S-1 + docetaxel as reported by Fujii et al. [36].

Cisplatin at a dose of 60 mg/m^2 on day 8 was combined with S-1 for 3-weeks-on and 2-weeks-off treatment [37]. This was repeated every 5 weeks, unless disease progression was observed. The RR was 74% (14/19; 95% confidence interval (CI) 54.9–90.6) and the MST was 383 days. Komatsu et al. [38] reported the results of a phase I/II study with CPT-11 + S-1 (IRIS study) in AGC patients. S-1 was given orally twice a day for 14 days and CPT-11 was administered as a 90-min intravenous infusion on days 1 and 15. This regimen was repeated every 4 weeks. The overall RR was 54.2% in the phase II study. The MST achieved with this regimen was 581 days. Yoshida et al. [39, 40] performed a phase I study and a phase II study of docetaxel in combination with S-1 in patients with AGC. In the phase II study, the RR was 52.1% and the MST was 434 days. Moreover, the biochemical modulations of docetaxel enhanced the sensitivity of 5-FU in vitro and in vivo [41]. More interestingly, the mTOR inhibitor downregulated the expression of TS and enhanced the reactivity of 5-FU on TMK-1 gastric cancer cells [42].

Based on the results obtained in the above phase II studies, 3 large randomized phase III studies, the SPIRITS trial [22], the TOP-002 trial [43] and the JACCRO GC03 trial [36, 44] were conducted independently to compare the data with that of S-1 monotherapy, the results of which are summarized in table 2.

In the SPIRITS trial, chemotherapy-naïve patients with AGC were randomly assigned to receive either S-1 plus cisplatin or S-1 alone. The primary end point was overall survival and the secondary end points were progression-free survival, proportion of responders and safety. Median overall survival was significantly longer in the patients assigned to receive S-1 plus cisplatin than in those assigned to receive S-1 alone (13.0 vs. 11.0 months, respectively; hazard ratio (HR) 0.77; 95% CI 0.61–0.98; $p = 0.04$). Progression-free survival was significantly longer in the patients assigned to receive S-1 plus cisplatin than in those assigned to receive S-1 alone (median progression-free survival 6.0 vs. 4.0 months, respectively; $p < 0.0001$). Moreover, of the 87 patients with target tumors assigned to receive S-1 plus cisplatin, 1 showed a complete response (CR) and 46 showed a partial response

Table 2. Review of phase III clinical trials in Japan

	S-1/ S-1 + CPT-11 (GC0301/TOP-002)	S-1/ CPT-11 + CDDP (JCOG 9912)	S-1/ S-1 + CDDP (SPIRITS trial)	S-1/ S-1 + docetaxel (START trial)
MST, months	10.5/12.8	11.4/12.3	11.0/13.0	11.0/13.0
1-year survival rate	45.0%/52.0%	49.7%/52.5%	46.7%/54.1%	46.0%/52.5%
2-year survival rate	22.5%/18.0%	–/–	15.3%/23.6%	20.6%/23.7%

(PR) (total RR 54%). Of the 106 patients with target tumors assigned to receive S-1 alone, 1 showed a CR and 32 showed a PR (total RR 31%). Based on this trial, S-1 plus cisplatin became regarded as a new standard first-line treatment for patients with AGC in Japan.

A randomized phase III trial was conducted to evaluate the efficacy and safety of IRIS (S-1 + CPT-11) versus S-1 alone for AGC. Patients with previously untreated AGC were randomized to arm A (oral S-1, 80 mg/m^2 on days 1–28, every 6 weeks) or arm B (IRIS: oral S-1, 80 mg/m^2 on days 1–21; intravenous CPT-11, 80 mg/m^2 on days 1 and 15, every 5 weeks) by dynamic allocation. As a result, 326 patients were randomized to arm A (162 patients) or arm B (164 patients), with a final 315 evaluable patients (160 in arm A and 155 in arm B). Although the MST of the arm A patients was 318 days (95% CI 286–395) and that of the arm B patients was 389 days (95% CI 324–458), arm B did not show significant superiority to arm A. The RRs were significantly different, being 26.9% in arm A versus 41.5% in arm B in 187 RECIST (Response Evaluation Criteria in Solid Tumors)-evaluable patients. Based on this trial, IRIS achieved MST and was better tolerated; however, it did not show significant superiority to S-1 alone in terms of the overall survival, and could thus not become a first-line treatment for AGC.

A randomized phase III study comparing S-1 alone with the S-1 + docetaxel combination was conducted through the JACCRO GC03 trial. This study was a prospective, multicenter, multinational (Korea and Japan), nonblinded, randomized, phase III study of patients with AGC. Patients were randomly assigned to receive 3-week cycles of treatment arm A (docetaxel and S-1) or 6-week cycles of treatment arm B (S-1 only). The primary objective of the study was to compare the median overall survival of the test arm (docetaxel and S-1) with that of the control arm (S-1 only). The secondary objectives were to assess the time to tumor progression (defined as the time from randomization to the date of first documentation of progressive disease), to determine the clinical response/RR (defined as the sum of the CR and PR according to RECIST criteria) and to evaluate the safety of the 2 regimens. It was expected that 628 patients (314 in each treatment arm) would be enrolled in this trial and this was exceeded, with confirmation of 628 patients from 103 centers in September 2008. Although the primary end point was not met, PR and RR were superior in the combination arm [44]. What is more interesting in this combination is that the docetaxel enhances the cytotoxic effect of 5-FU via biochemical modulations through decreased expression and activity of TS and dihydropyrimidine dehydrogenase and increased activity of orotate phosphoribosyltransferase [41]. It was recently reported that these effects can be modulated even more by molecular targeting agents including mTOR inhibitor [42].

The Role of Surgical Intervention in Stage IV Gastric Cancer Patients

Palliative and Volume Reduction Surgery

Gastric bypass, jejunostomy, ileostomies and colostomies are sometimes performed because of the pyloric stenosis of the primary tumor and/or tumors of the peritoneal disseminated disease of gastric cancer, and often, even if not by R0 resection, primary tumors are removed because of bleeding or obstruction of the stomach and bowels, all of which are regarded as palliative surgery. In the 1980s, the resection of the primary tumors and the removal of metastatic disease were often conducted as tumor volume reduction surgery. However, the prognosis of patients was not satisfactory because although the main treatment tool was palliative chemotherapy, the RR of chemotherapy regimens in those days was 20–30% and in the end, the patients died due to the tumor burden in spite of the reduction surgery. In order to improve the survival of the patients, new regimens or new chemotherapeutic