frequently found in advanced stage gastric cancer. To decrease the incidence of relapse after R0 resection, postoperative adjuvant chemotherapy is the standard treatment in Japan and Korea. The study known as Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer (ACTS-GC) demonstrated that S-1 is an effective adjuvant treatment for Japanese patients who have undergone D2 dissection for locally advanced gastric cancer.[6] In Korea, the capecitabine and oxaliplatin adjuvant study in stomach cancer (CLASSIC) trial showed the favorable result that capecitabine and oxaliplatin (XELOX) chemotherapy after curative resection of gastric cancer improves patient survival.[7]

S-1 is an oral fluoropyrimidine derivative developed in Japan, based on the concept of biochemical modulation. S-1 consists of tegafur, gimeracil, and oteracil potassium in a molar ratio of 1:0.4:1, respectively: tegafur, a prodrug that slowly metabolizes to 5-fluorouracil; gimeracil, which reversibly inhibits dihydropyrimidine dehydrogenase, the rate-limiting degrading enzyme of 5-fluorouracil, and thereby increases the plasma concentration of 5-fluorouracil; and oteracil potassium, which is distributed in high concentrations in gastrointestinal tissue and inhibits phosphorylation of 5-fluorouracil, thereby reducing gastrointestinal toxicity.[8] A more intensive regimen, such as S-1 plus cisplatin, has demonstrated a significantly higher response rate and longer survival than S-1 alone in the SPIRITS trial.[9]

Docetaxel (DTX) (Taxotere®, Sanofi-Aventis, Paris, France) is a semi-synthetic taxoid derived from the European yew tree, *Taxus baccata*. DTX also showed acceptable outcomes in patient trials both as a single agent and in combination with fluoropyrimidines or other agents. Enhanced antitumor activity was reported in a laboratory study of human gastric cancer xenografts treated with S-1 and DTX.[10,11] In previous phase II studies, favorable results were shown with the combination of S-1 and DTX for patients with advanced and recurrent gastric cancers.[12–14] In the present study, we hypothesized that preoperative chemotherapy combining DTX and S-1 (DS) in Stage III resectable advanced gastric cancer would induce a pathological response rate (pRR) of 40 %. The aim of this phase II study was to evaluate the feasibility and efficacy of this regimen and to select candidates for an experimental arm in the next phase III trial. Several phase II studies have demonstrated that a regimen of S-1 and cisplatin (SC) was safe and feasible in the neoadjuvant setting.[15–18] At present, the Japan Clinical Oncology Group (JCOG) is conducting a phase III trial of neoadjuvant chemotherapy using two courses of SC followed by surgery and postoperative S-1 as a test arm compared with surgery and postoperative S-1 as a control arm for scirrhous-type gastric cancer. Moreover, promising survival results were reported from a small phase II trial evaluating two courses of SC in the neoadjuvant setting for bulky nodal disease.[17] These phase II trials have shown favorable results for neoadjuvant chemotherapy for potentially unresectable gastric cancer; however, it has not been established whether neoadjuvant chemotherapy is necessary for the curative patient. This is the first phase II study of neoadjuvant chemotherapy with D2 gastrectomy for patients with clinical Stage III gastric cancer.

METHODS

Eligibility Criteria

Patients with histologically and cytologically confirmed adenocarcinoma of the stomach, diagnosed as Stage IIIa or Stage IIIb according to the Japanese classification of gastric carcinoma, 13th edition,[19,20] were included in this study if they met all of the following criteria: age >20 and ≤75 years; Eastern Cooperative Oncology Group performance status (ECOG PS) ≤1; able to take oral drug; and adequate hepatic, renal, respiratory, and bone marrow function. Staging laparoscopy was required to confirm no peritoneal dissemination. Written informed consent was obtained from all patients prior to enrollment in the study. Patient enrollment began in July 2007 and ended in November 2009. This study was approved by the Institutional Review Board of all institutions and was registered in the UMIN clinical trial registry (UMIN000000875).

Treatment Schedule

DTX (35 mg/m^2) was administered as a 1-h infusion on the morning of days 1 and 15 of each cycle (every 4 weeks). S-1 (40 mg/m^2) was given orally twice daily (within 30 mins after morning and evening meals) for 2 weeks, followed by a drug-free interval of 2 weeks. Patients received two cycles of DTX with S-1 (DS) therapy followed by surgery.

Surgery

A total or distal gastrectomy with D2 lymphadenectomy was performed. Involved adjacent organ(s), if any, were also removed to achieve R0 resection. A laparoscopic gastrectomy was not prescribed in the protocol. If resectable M1 disease (hepatic, peritoneal, and/or lymphatic metastases) was found during surgery, it was removed to achieve R0 resection. After the R0 resection, adjuvant chemotherapy with S-1 was initiated within 42 days after surgery. A 6-week course consisting of 4 weeks of daily oral S-1 administration at a dose of 80 mg/m^2/day followed by 2 weeks of rest was repeated during the first year after surgery.

Endpoints

The primary endpoint of the study was the pathological response rate (pRR). Assessment of pathological response

was determined centrally by two pathologists and graded according to the proportion of necrosis in the tumor: grade 0, no necrosis; grade 1a, <1/3 necrosis; grade 1b, >1/3 or <2/3 necrosis; grade 2, >2/3 or greater than all necrosis; and grade 3, all parts of the tumors affected by necrosis. The secondary endpoints were 3-year relapse-free survival (RFS), overall survival (OS) from the registration, and adverse effects. During the 4 weeks before chemotherapy was commenced, all patients underwent the following studies: physical examination, complete blood cell count, hepatic and renal function tests, and chest and abdominal computed tomography (CT) or magnetic resonance imaging (MRI). Physical examination, hepatorenal function tests, and blood counts were performed before every cycle. Patients were assessed before starting each 2-week cycle according to the National Cancer Institute Common Toxicity Criteria (CTC) Common Terminology Criteria for Adverse Events, version 3.0 (CTCAE vers. 3). Surgical completion was assessed according to the Clavien–Dindo classification. All enrolled patients were followed for 5 years. Physical and blood examinations were conducted every 3 months for the first 3 years and every 6 months for the last 2 years. An abdominal CT was performed at least every 6 months.

Statistical Considerations

A sample size of 45 was calculated according to a two-stage attained design of Green and Dahlberg, with one-sided significance level of 0.05 and 90 % power. By using a pRR of ≤20 % for the null hypothesis versus pRR of ≥40 % for an alternative hypothesis, 25 patients were recruited to the first stage. If five or more patients achieved pRR, the study would proceed to the second stage, with an additional 20 patients recruited. The null hypothesis would be rejected if 14 or more patients achieved pRR.

The confidence interval (CI) for the response rate was estimated by the Clopper-Pearson method. The duration of survival was measured from the day of gastrectomy, and the OS and RFS curves were calculated by the Kaplan–Meier method. All statistical analyses were performed using the SAS for Windows Release 9.3 (SAS Institute Inc., Cary, NC).

RESULTS

Patient Characteristics

A total of 47 patients from 14 centers were centrally registered between November 2007 and November 2009. All patients were eligible for analysis. The performance status (PS) was 0 in 41 patients, and one in six. Baseline patient characteristics are listed in Table 1. Forty-six patients (98 %) underwent surgery, and curative resection was performed in 44 patients. The treatment protocol was completed in 44 patients (93.6 %) of the total patient population, but only 37 (78.7 %) of those who underwent curative resection. All 47 patients underwent tumor resection (curative, 44; noncurative, three). The surgical methods were total gastrectomy ($n = 31$), distal gastrectomy ($n = 15$), and proximal gastrectomy ($n = 1$). Concomitant resection of the spleen was performed in 12 patients.

Clinical and Pathological Response

The response to preoperative chemotherapy using Response Evaluation Criteria in Solid Tumors (RECIST) was 34 %. Stable disease (SD), progressive disease (PD), not evaluable (NE) were 51, 4.3, and 10.6 %, respectively (Supplementary Table 1). Pathological responses are listed in Table 2. Pathological response, the primary endpoint (grade 1b to 3), was observed in 46.8 % of primary lesions. The overall response rate, as determined by the independent committee, was 46.8 %, with a 90 % CI of 34.2–59.7 %.

TABLE 1 Baseline patient characteristics ($N = 47$)

Factor		$N = 47$
Age (range)		63 (37–79)
Gender (male/female)	Male	36
	Female	11
Performance status	0	41
	1	6
Location of tumor	U	11
	M	19
	L	16
T stage	T2	4
	T3	38
	T4	5
Borrmann macroscopic type	2	13
	3	24
	4	9
	5	1
N stage	0	1
	1	30
	2	16
Clinical stage	IIIA	31
	IIIB	16
Histological type	Intestinal	13
	Diffuse	34

L lower, *M* middle, *N1* metastasis to D1 regional lymph nodes, *N2* metastasis to D2 regional lymph nodes, *T2* tumor invades the muscularis propria or subserosa, *T3* tumor invasion extends to or beyond the serosa, *T4* tumor invades adjacent structures (SI), *U* upper

TABLE 2 Pathological efficacy

Grade	Full analysis set	($N = 47$) (%)
0	0	0
1a	24	51.0
1b	7	14.9
2	13	27.2
3	2	4.3
Unresectable	1	2.1
Pathological response rate (grade 1b, 2, 3)	22	(47 [34.2–59.7])

Grade 0, no necrosis; grade 1a, <1/3 necrosis; grade 1b, >1/3 or <2/3 necrosis; grade 2 > 2/3 or greater than all necrosis; grade 3, all parts of the tumors affected by necrosis

Toxicity and Tolerability

The most common toxicities of neoadjuvant chemotherapy were grade 3/4 neutropenia (42.6 %), leukopenia (17.0 %), anorexia (8.5 %), febrile neutropenia (6.4 %), nausea (4.3 %), neuropathy (4.3 %), and allergic reaction (4.3 %) (Table 3). Seven patients did not complete the neoadjuvant therapy due to allergic reactions ($n = 2$), grade 3 anorexia ($n = 1$), grade 2 nausea and anorexia ($n = 2$), and PD ($n = 2$); all seven patients had gastrectomy). Among patients who received preoperative DTX with S-1 (DS) therapy, surgical complications developed in 19 patients (40.4 %) (Supplementary Table 2). The number of complications according to the Clavien–Dindo classification was 3 for grade I, 10 for grade II, and 9 for grade IIIa. The most frequent complication, pancreatic juice leakage, developed in eight patients (17.0 %), and the next most frequent complication, intra-abdominal abscess requiring drainage therapy, developed in six patients (12.8 %). No patient suffered from severe surgical complications of grade IIIb or higher. No patients died due to surgical complications.

Survival After Resection

After a median follow-up of 3 years, the median relapse-free survival (RFS) and overall survival (OS) was not reached (Fig. 1a, b). RFS was assessed for 44 patients who underwent gastrectomy, and OS was assessed for all 47 patients. The 3-year RFS rate was 53.2 % (95 % CI 19.4 % to not estimable) in 44 assessable patients, and 3-year OS was 60.9 % (95 % CI 28.1 % to not estimable) in 47 assessable patients. When the survival rate was separated by pRR, the 3-year RFS rate of grade 1b/2/3 cases was 62.9 %, whereas that of grade 0/1a cases was 42.9 % (Fig. 2a). The OS of grade 1b/2/3 cases and grade 0/1a cases were 72.7 and 52.2 %, respectively (Fig. 2b). Because of the small sample size, this difference in OS was not statistically significant (hazard ratio = 0.45).

DISCUSSION

Neoadjuvant chemotherapy is commonly administered for advanced, but resectable cancer to diminish the undetected cancer cells. In Europe, preoperative and postoperative (perioperative) chemotherapy is the standard treatment for advanced gastric cancer because the perioperative combination chemotherapy of epirubicin, cisplatin, and infused fluorouracil (ECF) improved survival in patients with locally advanced gastric cancer in a phase III trial.[21] Another phase III trial showed a survival advantage of 5-flurouracil and cisplatin (FP) perioperative

TABLE 3 Treatment-related adverse events

Adverse events	Grade 1*	Grade 2	Grade 3	Grade 4	Incidence (%)	Incidence of grade 3/4 (%)
Hematological toxicity						
Leukopenia	12	18	7	1	80.9	17.0
Neutropenia	1	8	16	4	61.7	42.6
Hemoglobin	27	14	1	0	68.1	2.1
Non-hematological toxicity						
Anorexia	19	6	4	0	61.7	8.5
Nausea	15	4	2	0	44.7	4.3
Vomiting	5	2	0	0	14.9	0
Allergic reaction	3	1	0	2	12.8	4.3
Diarrhea	5	1	0	0	12.8	0
Neuropathy	2	1	2	0	10.6	4.3
Febrile neutropenia	—	—	3	0	6.4	6.4

*Adverse effect was assessed according to the National Cancer Institute Common Toxicity Criteria (CTC) Common Terminology Criteria for Adverse Events version 3.0 (CTCAE vers. 3)

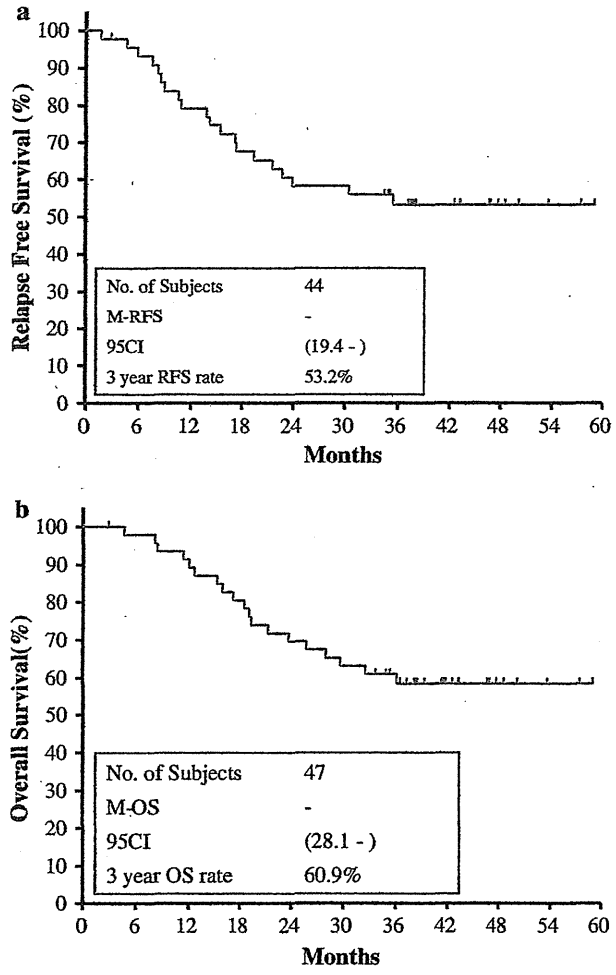

FIG. 1 After a median follow-up of 3 years, the median relapse-free survival (RFS) and overall survival (OS) was not reached. **a** RFS. **b** OS. *95 CI* 95 % confidence interval, *M-OS* median overall survival, *M-RFS* median relapse-free survival, *NR* not reached

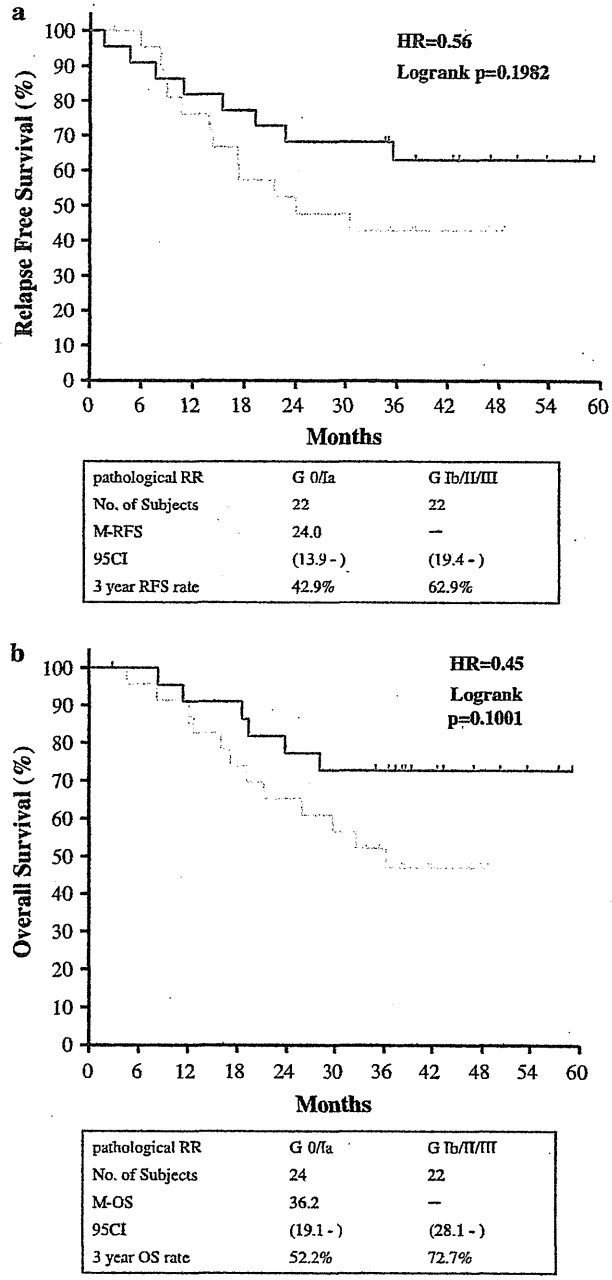

FIG. 2 Patients with high pathological response had improved relapse-free survival (RFS) and overall survival (OS) compared with those for patients with low pathological response. **a** The RFS of each subset of pathological response. The *solid line* represents the survival of the high pathological response group with grade 1b/2/3 (G 1b/2/3) pathological response. The *dotted line* represents the survival of the pathological response group with grade 0/1a (G 0/1a) pathological response. **b** The OS of each subset of pathological response. The *solid line* represents the survival of the high pathological response group with grade 1b/2/3 (G 1b/2/3) pathological response. The *dotted line* represents the survival of the pathological response group with grade 0/1a (G 0/1a) pathological response. One patient could not be assessed for pathological response. *95 CI* 95 % confidence interval, *HR* hazard ratio, *M-OS* median overall survival, *M-RFS* median relapse-free survival, *NR* not reached, *RR* response rate

chemotherapy for resectable gastric cancers.[22] The patient enrollment criteria of these European clinical trials included lower esophageal cancer, and D2 gastrectomy was not conducted in all patients. In Asian countries, D2 gastrectomy is the standard treatment for gastric cancer, and neoadjuvant chemotherapy has not been used for advanced, but resectable cancers. In Japan, it has been proven that overall survival and disease-free survival are improved by adjuvant S-1 monotherapy in advanced gastric cancer.[5] It has not been established that neoadjuvant chemotherapy is safe and effective for patients who have resectable advanced gastric cancers, who undergo D2 gastrectomy

We conducted this phase II trial of neoadjuvant chemotherapy for patients with advanced gastric cancer who could be resected with standard D2 gastrectomy. The objective of this clinical trial was to test the safety and effectiveness of neoadjuvant docetaxel and S-1

combination chemotherapy. Because exact evaluation of cancer staging before treatment was necessary to conduct a clinical trial of neoadjuvant chemotherapy for Stage IIIA or Stage IIIB patients, staging laparoscopy was required for all cases before enrollment. As a result, no patients were diagnosed with peritoneal dissemination at the planned operation.

In this study, operative complications were assessed in addition to chemotherapy-related adverse effects. The most common toxicities of neoadjuvant chemotherapy were grade 3/4 neutropenia (42.6 %) and leukopenia (17.0 %), similar to those in previous reports.[12,14] Seven patients did not complete the neoadjuvant therapy because of adverse effects. Abdominal abscess and pancreatic juice leakage were the most frequent surgical complications, but all cases recovered without reoperation. Anastomotic leakage was not experienced, but the incidence of abdominal abscesses was slightly higher than that expected with D2 operation.[4] Treatment-related death and operative mortality were not observed in this study. This differs from the JCOG0001 study, which reported 5 % treatment-related death and 2 % operative mortality. We conclude that neoadjuvant DTX with S-1 (DS) chemotherapy can be used safely. The DS therapy has several advantages for neoadjuvant chemotherapy. This therapy can be adopted at outpatient clinics. Inpatient care was not necessary for most patients in this trial. It is necessary to be in the hospital if cisplatin (CDDP) is used for neoadjuvant chemotherapy because hydration is usually needed. In this study, renal function was not damaged in any patient, despite outpatient clinic treatment. This is an important factor to consider for neoadjuvant chemotherapy.

To show the effectiveness of neoadjuvant chemotherapy for advanced gastric cancer patients, we chose pathological RR (pRR) as the primary endpoint. Phase II studies of docetaxel and S-1 combination therapy for unresectable and recurrent gastric cancer were previously conducted, and the RR was reported as 40–56 %.[12,14,23] However, there has been no such clinical study evaluating resectable gastric cancer. For resectable gastric cancer, the evaluation of clinical response using Response Evaluation Criteria in Solid Tumors (RECIST) was quite difficult. Therefore, pRR was chosen as the primary endpoint in this study. The pRR was one of best surrogated endpoints for neoadjuvant chemotherapy for gastric cancer.[24] The pathological response (grade 1b or greater) of JCOG 0001, a phase II trial of neoadjuvant chemotherapy for locally advanced gastric cancer, was 7 of 55 patients (12.7 %).[17] Tsuburaya et al.[15] reported that grade 1b or greater pRR was observed in 18 of 42 patients (42.8 %) on paclitaxel and cisplatin neoadjuvant therapy.[15] In a preoperative setting, a phase II study of S-1 plus cisplatin for patients with locally advanced gastric cancer (JCOG0210) showed 48 % pRR in the primary lesion.[25] In our study, grade 1b or greater was observed in 22 of 47 patients (46.8 %). The mean pRR was 46.8 % among the 47 patients, which was higher than the expected pRR of 40 %. The lower end of the 95 % CI for pRR was 34.2 %, which also exceeded the threshold pRR of 20 %. This response was similar to the previous neoadjuvant study for patients with far advanced gastric cancer. This study also showed that patients with high pathological response had improved relapse-free survival and overall survival compared with those for patients with low pathological response (Fig. 2). Although the sample size was too small to show statistical significance of pathological response on patient survival, this is a very promising result for the treatment of gastric cancer. In addition, it is possible that the assessment of pathological response showed the chemosensitivity of postoperative chemotherapy. The preoperative chemotherapy regimen included docetaxel and S-1. On the other hand, S-1 monotherapy was only used as postoperative chemotherapy in our study. Therefore, postoperative DS therapy may play a role in improving RFS and OS in patients who show high response to neoadjuvant therapy. Recently, the monoclonal antibody trastuzumab has become the standard treatment for human epidermal growth factor receptor 2 (HER2)-positive advanced gastric cancer. In the future, combination therapy with trastuzumab and DTX with S-1 (DS) should be considered for patients with HER2-positive tumors.

In conclusion, preoperative DS therapy was highly active against resectable clinical Stage III gastric cancer, and this treatment was well tolerated with few toxicities. The favorable results of our study have raised expectations that this therapy may improve survival outcomes for patients with advanced gastric cancer.

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ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Induction of a Pathological Complete Response by Four Courses of Neoadjuvant Chemotherapy for Gastric Cancer: Early Results of the Randomized Phase II COMPASS Trial

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ABSTRACT

Background. The prognosis for stage 3 gastric cancer is not satisfactory, even with S-1 adjuvant chemotherapy. A randomized phase II trial was conducted to compare two and four courses of neoadjuvant S-1/cisplatin (SC) and paclitaxel/cisplatin (PC) using a two-by-two factorial design for locally advanced gastric cancer. The primary endpoint was overall survival. We clarified the impact of these regimens on the secondary endpoints, including the clinical and pathological responses, chemotherapy-related toxicities, and surgical results.

Methods. Patients received S-1 (80 mg/m^2 for 21 days with 1 week's rest)/cisplatin (60 mg/m^2 at day 8) or paclitaxel/cisplatin (80 and 25 mg/m^2, respectively, on days 1, 8, and 15 with 1 week's rest) as neoadjuvant chemotherapy.

Results. Eighty-three patients were assigned to arm A (two courses of SC, $n = 21$), arm B (four courses of SC, $n = 20$), arm C (two courses of PC, $n = 21$), and arm D (four courses of PC, $n = 21$). Pathological response rate was 43 % in arm A, 40 % in arm B, 29 % in arm C, and 38 % in arm D. Pathological complete response was only observed in arms B (10 %) and D (10 %). Most bone marrow toxicities, nausea, vomiting, alopecia, and fatigue were slightly higher but acceptable in arms B and D. Grade 3/4 surgical morbidities were not commonly observed in all four arms.

Conclusions. Pathological complete response could be induced by four courses of neoadjuvant chemotherapy without a marked increase of toxicities, regardless of a SC or PC regimen.

Gastric cancer remains the second leading cause of cancer death worldwide.[1] For locally advanced disease, the standard treatment is chemotherapy and D2 gastrectomy in Asia, D2 plus postoperative chemotherapy with S-1 for 1 year in Japan, and D2 plus postoperative chemotherapy with capecitabine and oxaliplatin for around 6 months in Korea.[2–5] However, even with D2 gastrectomy and

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adjuvant chemotherapy with S-1, the prognosis of stage 3 tumors is not satisfactory.[6] In contrast to the use of adjuvant S-1 chemotherapy for 1 year in Japan, other approaches have been established in Western countries. Pre- and postoperative chemotherapy is a standard treatment in Europe.[7–9] Pre- or postoperative chemoradiation with D2 is frequently selected in the United States.[10]

Combination chemotherapy using S-1 plus cisplatin (SC) is a standard regimen administered for metastatic gastric cancer in Japan.[3,11] However, SC was not tolerable when it was started just after surgery, but was feasible and safe when provided preoperatively.[12–16] Paclitaxel is another key drug used for metastatic disease and has been tested in an adjuvant setting in a phase III trial.[17–19] Moreover, paclitaxel plus cisplatin (PC) demonstrated a high response rate and feasibility for metastatic disease.[17,20] Furthermore, PC achieved a high pathological response rate with acceptable toxicity in the neoadjuvant setting.[21] Both SC and PC are promising regimens for neoadjuvant chemotherapy; however, a suitable duration of treatment has not yet been established. Two courses have been selected in most Japanese studies, while three courses were adopted in the MAGIC phase III trial, which confirmed its survival benefit.[7,14,22] In contrast to neoadjuvant chemotherapy, the patients received S-1 for 1 year or capecitabine plus oxaliplatin for 6 months in the postoperative adjuvant setting after undergoing D2 gastrectomy.[4,5]

On the basis of these previous studies, a randomized phase II trial was conducted to compare neoadjuvant chemotherapy using two and four courses of SC and PC with a two-by-two factorial design for macroscopically resectable locally advanced gastric cancer.[23] The primary endpoint was overall survival (OS). The present study was a randomized phase II trial, which aimed not to draw definite conclusion but to select better regimen and course for the next phase III trial. This report clarified the impact of these regimens on early endpoints, including the clinical and pathological responses, chemotherapy-related toxicities, and surgical results.

PATIENTS AND METHODS

Eligibility Criteria

The eligibility criteria were as follows: (1) histologically proven gastric adenocarcinoma, (2) T2–3/N+ or T4aN0 in case of scirrhous or junctional tumors, T2–3 with nodal metastasis to the major branched artery, T4aN+ , T4b, paraaortic nodal metastases, or resectable minimal peritoneal metastases confirmed by laparoscopy, (3) no other distant metastasis, (4) age between 20 and 80 years, (5) Eastern Cooperative Oncology Group performance status of 0 or 1, (6) no previous treatment, (7) sufficient organ functions (white blood cell count >4,000/mm^3 and <12,000/mm^3, neutrophil count >4,000/mm^3, hemoglobin >8.0 g/dl, platelet count >100,000/mm^3, GOT <100 IU, GPT <100 IU, total bilirubin <1.5 mg/dl, creatinine clearance >30 mg/dl/h according to measured value or Cockcroft–Gault formula, no ischemic change or ventricular arrhythmia by exercise ECG), and (8) written informed consent provided. The exclusion criteria were as follows: (1) serious comorbidities, (2) synchronous or metachronous cancer (synchronous multiple cancers in the stomach included), (3) acute inflammation, (4) systemic treatment with a corticosteroid, (5) hypersensitivity to Cremophor EL, (6) pregnant or breast-feeding women, or women who were contemplating pregnancy, (7) mental disorders, (8) medical history of allergy or hypersensitivity to any drugs, (9) history of alcoholic anaphylaxis, (10) peripheral neuropathy, and (11) patients judged to be inappropriate for the study by the physicians.

The clinical diagnosis of the T and N stages was basically determined by thin-slice CT or multidetector row CT following Habermann's method.[24] Briefly, T4a tumors were defined as transmural tumors with obvious blurring of at least one-third of the tumor extent, or wide reticular strands surrounding the outer border of the tumor. Regional lymph nodes were considered to be involved by metastases if they were larger than 8 mm in the short-axis diameter. Staging laparoscopy was mandatory to diagnose peritoneal metastasis. Our previous study demonstrated that the accuracy was 71.4 % for T staging and 75.9 % for N staging according to the same method and criteria.[25]

Preoperative Chemotherapy

In the SC regimen, S-1 was provided twice a day for a total of 80 mg/m^2 for the first 3 weeks of a 4-week cycle, and cisplatin was provided as an intravenous infusion of 60 mg/m^2 on day 8 of each cycle, as described previously.[11] In the PC regimen, paclitaxel 60 mg/m^2 and cisplatin 25 mg/m^2 were administered on days 1, 8, and 15 as one course, which was repeated every 4 weeks.[20] The dose modification criteria were based on the previous studies.[11,21] Neoadjuvant chemotherapy was discontinued if there was documented disease progression, unacceptable toxicity, or withdrawal of consent.

Surgery

During the 2–6 weeks after completion of the neoadjuvant chemotherapy or when the tumors progressed during the treatment, patients proceeded to surgery on the basis of the criteria defined by the protocol. After laparotomy, the resectability was evaluated. Intraperitoneal wash cytology was mandatory. R0 resection was aimed for by gastrectomy with standard D2 lymphadenectomy.[3] D3 dissection or

combined resection of a small part of the peritoneum or adjacent organs were permitted for curative intent. Depending on the location of the primary tumor, the surgeon performed either a total or distal subtotal gastrectomy. In total gastrectomy for proximal tumors, the spleen was removed in principle for splenic hilar lymphadenectomy.

After a macroscopic curative resection was achieved, the patients were strongly recommended to undergo postoperative chemotherapy using S-1 for more than 6 months until 12 months, as long as the tumors did not recur. Any adjuvant treatment other than S-1 was not permitted until a recurrence developed.

Registration and Randomization

Eligible patients were registered into the data center of this study and then randomized as follows: arm A, two courses of SC; arm B, four courses of SC; arm C, two courses of PC; and arm D, four courses of PC. Randomization was performed by a centralized dynamic method using the following factors: scirrhous type including giant type 3 (yes or no), tumor invasion of the esophagus (yes or no), clinical stage 2–3b or 4, creatinine clearance (<60 or ≥60 mg/m^2/min), and institution as balancing variables.

Study Design and Statistical Methods

The present study was an open-label, randomized phase II trial of selection design as proposed by Simon.[26] The primary endpoint was the 3-year OS rate. The early key secondary endpoints were the incidence of adverse events, pathological response rate, clinical response rate, and R0 resection rate. The sample size was calculated on the hypothesis that the 3-year OS rate was expected to be between 20 and 40 % for each reference arm of the two courses and SC regimen. When each test arm of four courses and PC regimen achieved 10 % improvement of the 3-year OS rate, the statistical power (selection probability) was calculated to be 0.81, 0.79, and 0.78 for a total sample size of 60, and it was calculated to be 0.85, 0.83, and 0.82 for a total sample size of 80. Considering these calculations, the number of patients to be accrued was set at 60–80 in total.

The progression of tumors was evaluated by the 7th edition of the International Union Against Cancer tumor, node, metastasis classification system.[27] The clinical response was evaluated by the first version of the Response Evaluation Criteria for Solid Tumors.[28] Surgical specimens were pathologically evaluated as grade 0 when there was no degeneration and/or necrosis within the tumor, grade 1a when the area was less than one-third of the tumor, grade 1b when the area was more than one-third and less than two-thirds, grade 2a when the area was more than two-thirds but tumor tissues were apparently remained, grade 2b when only minimal tumor cells remained, and grade 3 when there was no residual tumor.[3] Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria (version 3.0). The severity of surgical morbidity was evaluated by the Clavien–Dindo classification.[29]

The protocol was approved by the institutional review boards/ethics committees of each participating institution. This trial was registered in the University Hospital Medical Information Network (UMIN) center (ID UMIN00000 2595).

RESULTS

Patients

Between October 2009 and July 2011, a total of 83 patients were assigned to arm A (two courses of SC, n = 21), arm B (four courses of SC, n = 20), arm C (two courses of PC, n = 21), and arm D (four courses of PC, n = 21). All patients were eligible and received neoadjuvant chemotherapy. Table 1 shows the patient demographics and tumor characteristics.

The actual courses were defined as one course when cisplatin (CDDP) was provided at least one time during one course. The rate of completion of neoadjuvant chemotherapy was 91 % (19 of 21) in arm A, 60 % (12 of 20) in arm B, 100 % (21 of 21) in arm C, and 81 % (17 of 21) in arm D. The rate of completion of chemotherapy was 76 % (31 of 41) in the SC arm compared to 90 % (38 of 42) in the PC arm, and 95 % (40 of 42) in the two-course arm compared to 71 % (29 of 41) in the four-course arm. A total of six patients did not proceed to surgery because of disease progression. Among the patients who proceeded to surgery, two patients in arm C received a bypass operation because of peritoneal metastasis. Five patients underwent an R2 resection because of peritoneal metastasis, and eight patients had an R1 resection as a result of positive peritoneal cytology. All patients without peritoneal metastasis and positive peritoneal cytology received a D2 gastrectomy. The R0 resection rate was 81 % (17 of 21) in arm A, 75 % (15 of 20) in arm B, 67 % (14 of 21) in arm C, and 76 % (16 of 21) in arm D. The R0 resection rate was 78 % (32 of 41) in the SC arm and 71 % (30 of 42) in the PC arm, while it was 74 % (31 of 42) in the patients treated with two courses and 76 % (31 of 41) in the patients treated with four courses. A flow diagram of the patients is provided in Supplementary Appendix Fig. A1.

TABLE 1 Patient characteristics

Characteristic	Variable	Arm A ($n = 21$)	Arm B ($n = 20$)	Arm C ($n = 21$)	Arm D ($n = 21$)
Age	Median	66	63	66	67
	Range	32–79	47–76	55–80	43–77
Gender	M/F	14/7	12/8	17/4	15/6
Performance status	0/1	21/0	20/0	20/1	20/1
Macroscopic type	Non-scirrhous	15	15	15	12
	Type 4/giant type 3	6	5	6	9
Histological type	Differentiated	8	9	11	8
	Undifferentiated	13	11	10	13
Clinical T	T2	0	0	0	1
	T3	1	1	2	2
	T4a	17	19	17	15
	T4b	3	0	2	3
Clinical N	N0	1	4	3	4
	N1	12	7	8	8
	N2	8	9	9	9
	N3	0	0	1	0
Clinical M	Negative	18	17	17	18
	Positive	3	3	4	4
Site of M	P or CY	3	3	3	4
	Para-aortic nodes	0	0	1	0

Response

Twenty-four patients had only nonmeasurable lesions and 59 had measurable lesions. The overall clinical response, evaluated among all 83 patients, was 43 % (9 of 21) in arm A, 50 % (10 of 20) in arm B, 24 % (5 of 21) in arm C, and 29 % (6 of 21) in arm D (Supplementary Appendix Table A1). The response rate was 46 % (19 of 41) in the SC arm and 26 % (11 of 42) in the PC arm, while it was 33 % (14 of 42) in the patients treated with two courses and 39 % (16 of 41) in those treated with four courses. The non-PD rate was 93 % (38 of 41) in the SC arm and 93 % (39 of 42) in the PC arm, while it was 95 % (39 of 41) in the patients treated with two courses and 90 % (38 of 42) in those treated with four courses.

Table 2 indicates the pathological response of the primary tumor. The pathological response rate, defined as tumor regression by more than two-thirds was 43 % (9 of 21) in arm A, 40 % (8 of 20) in arm B, 29 % (6 of 21) in arm C, and 38 % (8 of 21) in arm D. The pathological response rate was 42 % (17 of 41) in the SC arm and 33 % (14 of 42) in the PC arm, while it was 36 % (15 of 42) in the patients treated with two courses and 39 % (16 of 41) in those treated with four courses. The pathological complete response rate was 0 % (0 of 21) in arm A, 10 % (2 of 20) in arm B, 0 % (0 of 21) in arm C, and 10 % (2 of 21) in arm D. The pathological complete response rate was 0 % with a 95 % confidence interval from 0 to 8 % in the two-course arm and 10 % with a 95 % confidence interval from 3 to 23 % in the four-course arm. The P value for this comparison according to Fisher's exact test was 0.055. All patients who experienced pathological complete response had no tumor cells in either the primary tumor or the lymph nodes dissected. All patients who exhibited a pathological complete response completed four courses of chemotherapy.

Chemotherapy-Related Toxicities

The most frequently detected toxicities (all grades) in the SC arm were anemia in 33 patients (81 %), followed by neutropenia in 26 (63 %), appetite loss in 24 (59 %), leukocytopenia in 21 (51 %), fatigue in 15 (37 %), and nausea in 15 (37 %), while those in the PC arm were anemia in 37 patients (88 %), followed by leukocytopenia in 33 (79 %), nausea in 17 (41 %), alopecia in 14 (33 %), anorexia in 16 (38 %), and hyperkalemia in 16 (38 %). Most bone marrow toxicities, nausea, vomiting, alopecia, and fatigue were slightly higher, but still acceptable, in the four-course arms, regardless of the regimen. Grade 3/4 toxicities were not frequently observed for either the SC or PC regimen. Grade 3/4 nonhematological toxicities occurred in less than 10 % of patients in all arms (Supplementary Appendix Table A2).

TABLE 2 Pathological response of primary tumor

Characteristic	Arm A ($n = 21$)	Arm B ($n = 20$)	Arm C ($n = 21$)	Arm D ($n = 21$)
Grade 0	1	5	2	2
Grade 1a	10	5	10	9
Grade 1b	2	1	2	2
Grade 2a	5	3	4	4
Grade 2b	2	2	0	0
Grade 3	0	2	0	2
Unknown	0	0	0	0
Unresected	1	2	3	2

Surgery

Table 3 shows the details of the surgical procedure performed. Most patients received total gastrectomy and D2 dissection. More than half of the patients who received D2 total gastrectomy received splenectomy. D1 dissection was only selected when the patients had peritoneal metastasis or positive peritoneal cytology.

The surgical morbidity (all grade) is shown in Table 4. Grade 3 morbidities included anastomotic leakage, which occurred in 5 % of the patients in arms A and C, pancreatic fistula, abdominal abscess, and pyothorax, each of which occurred in 5 % of the patients in arm C, and postoperative hemorrhage in 6 % of the patients in arm B. Readmission was observed in one patient from arm C. None of the patients required reoperation. No surgical mortality was observed.

TABLE 3 Surgical findings

	Arm A	Arm B	Arm C	Arm D
Proceeded to surgery				
n	20	18	20	19
Bypass				
n	0	0	2	0
Gastrectomy				
Total	15	14	16	13
Distal	5	4	2	6
Dissection				
D1	2	2	2	0
D2	18	16	16	19
Combined organ resection				
Spleen	9	7	10	11
Gallbladder	1	4	4	2
Transverse colon	1	0	2	2
Pancreas	0	0	0	2
Diaphragm	0	1	1	0
Liver	0	1	0	0
Bleeding, g				
Median	365	470	468	320
Range	60–1280	0–1300	120–1560	70–1990
Time, min				
Median	256	239	253	254
Range	155–395	176–422	162–380	172–381

DISCUSSION

To our knowledge, the present study is the first randomized trial to compare the duration of neoadjuvant chemotherapy for locally advanced gastric cancer. The major finding of this study was that a high pathological complete response rate of 10 % was only achieved when four courses of neoadjuvant chemotherapy were completed. Although the comparison of the pathological complete response did not reach statistical significance, the result was highly suggestive because this trial was a randomized study and there was no bias in the background. So far, such a high pathological complete response rate has never been reported from any other studies using one, two, or three courses of neoadjuvant chemotherapy for gastric cancer.[7,9,14–16,22]

Even though the pathological response was almost equivalent between the two- and four-course arms, as well as between the SC and PC regimens, a pathological complete response was observed only in 10 % of the patients treated with four courses, regardless of the regimen. The patients were well randomized to each arm in terms of the background of the patients and tumor characteristics. The compliance with chemotherapy was similar in both the two- and four-course arms. Therefore, an accidental imbalance of patients, tumors, or chemotherapy could not explain the fact that this high pathological complete response was only observed in patients who received four courses of chemotherapy. These results indicated that a pathological complete response was induced by the addition of third and fourth courses. Previously, several investigators reported that the pathological response clearly separated the survival of gastric cancer patients who received neoadjuvant chemotherapy.[30,31] However, it was unclear whether the patients who experienced a pathological complete response had different survival from those who experienced a partial response. Our study will clarify the answer to this question in the future.

In contrast to the pathological response, only one patient (in arm B) exhibited a clinical complete response. A clinical complete response is a rare event in gastric cancer chemotherapy. Previously, a clinical complete response was reported in one of 87 metastatic gastric cancer patients who received SC and also in one of 49 metastatic patients who received a PC regimen.[11,20] The discrepancy between the pathological and clinical responses may be explained

TABLE 4 Surgical morbidity

Proceeded to surgery	Arm A		Arm B		Arm C		Arm D	
	($n = 20$)		($n = 18$)		($n = 20$)		($n = 19$)	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Postoperative bleeding	2	0	1	1	1	0	0	0
Anastomotic leakage	1	1	0	0	2	1	0	0
Pancreas fistula	1	0	3	0	2	1	3	0
Abdominal abscess	1	0	0	0	2	1	0	0
Wound infection	0	0	0	0	0	0	0	0
Ileus	0	0	0	0	0	0	0	0
Anastomotic stenosis	0	0	1	0	0	0	0	0
Pneumonia	0	0	1	0	0	0	0	0
Pyothorax	0	0	0	0	1	1	0	0

by the difficulties in evaluating patients for a clinical complete response. The response of the primary tumor is hard to be evaluated clinically, as the primary tumor is generally a nonmeasurable lesion. In three patients who exhibited a pathological complete response of lymph nodes in this study, the lymph nodes that had been considered to be occupied by the tumor were replaced by connective tissue but were not reduced in size. This is the reason why these three patients were not diagnosed with a clinical complete response of lymph nodes.

The chemotherapy-related toxicities increased when patients were treated with four courses compared to two. Most bone marrow toxicities, nausea, vomiting, alopecia, and fatigue were more frequently observed in those provided four courses than in those provided two courses of therapy, regardless of the regimen. However, the grade 3/4 toxicities were acceptable in the four-course arms of both regimens. No chemotherapy-related death was observed. On the other hand, surgical morbidities were not frequently observed in all four arms. Moreover, grade 3/4 complications were rare. No surgical mortality was observed. Thus, the administration of four courses of a SC or PC regimen, followed by surgery, appears to be feasible and safe.

Another concern in the four-course arm is the loss of a chance to receive R0 resection as a result of tumor progression during long-term chemotherapy. In the present study, the R0 resection rate was not low in the four-course arm compared with that observed in the two-course arm. Moreover, no patients exhibited disease progression during the third or fourth courses of chemotherapy. Tumor progression was observed during the initial two courses only. Although the rate of completing neoadjuvant chemotherapy was slightly lower in the four-course arm than in the two-course arm, the substantial difference was interpreted to be due to the toxicities observed in a few patients during the third and fourth courses. These results strongly suggest that compliance with chemotherapy was similar between the two- and four-course arms. When comparing the SC and PC regimens as neoadjuvant chemotherapy, both the radiological and pathological response rates were slightly lower in the PC arm than in the SC arm. However, the rates of R0 resection and pathological complete response were almost equivalent. The chemotherapy-related toxicities were feasible and safe in both regimens. The surgical morbidity was also low regardless of the regimen. The long-term survival results of the present study will clarify which regimen is better for neoadjuvant chemotherapy for gastric cancer.

This study included patients with para-aortic nodal metastases or resectable minimal peritoneal metastases. Para-aortic nodal metastasis is classified as M1 but is curable with neoadjuvant chemotherapy and surgery. Two phase II trials of neoadjuvant chemotherapy clarified that a high 3-year survival rate was obtained with neoadjuvant chemotherapy: 27 % with two courses of CPT-11 plus CDDP and 58.8 % with two courses of S-1 plus CDDP.[22,32] On the other hand, a peritoneal lavage cytology positive (CY1) status is also classified as M1 and is also curable with surgery and adjuvant chemotherapy containing S-1. Kodera and coworkers[33] reported that a 2-year survival rate of 46 % was obtained with surgery and S-1 therapy in patients with CY1. Without staging laparoscopy, CY1 or minimally resectable peritoneal metastasis is treated as clinically resectable disease. From the viewpoint of the prognosis and treatment strategy, para-aortic nodal metastases or resectable minimal peritoneal metastases are similar candidates for a trial of neoadjuvant chemotherapy for locally resectable advanced M0 disease.

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REVIEW ARTICLE

Neoadjuvant chemotherapy for gastric cancer in Japan: a standing position by comparing with adjuvant chemotherapy

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Abstract Adjuvant chemotherapy aims to eradicate micrometastatic tumor cells before and after curative surgery. Many Phase III trials have been conducted to study the efficacy of postoperative adjuvant chemotherapy; however, most trials have failed to show any survival benefit because of their low statistical power and/or poor patient compliance. Since 2000, two pivotal Phase III trials, the ACTS-GC and the CLASSIC, have demonstrated the efficacy of postoperative adjuvant chemotherapy following D2 gastrectomy. Although treatment with S-1 for 1 year or combination therapy with capecitabine and oxaliplatin for 6 months is effective, more intensive chemotherapy is necessary to further improve the survival rates. In Europe, two Phase III trials, the MAGIC and the FNCLCC/FFCD, have produced results that strongly suggest that neoadjuvant chemotherapy is beneficial. The advantages of neoadjuvant chemotherapy include a high rate of R0 resection, tumor regression, high compliance and the avoidance of unnecessary surgery. The disadvantage of neoadjuvant chemotherapy is over-diagnosis. In Japan, the Japan Clinical Oncology Group has conducted several clinical trials using neoadjuvant chemotherapy to target extensive nodal disease and/or scirrhous carcinomas. The optimal courses and regimens of neoadjuvant chemotherapy should, therefore, be clarified in the future.

Keywords Gastric cancer · Neoadjuvant chemotherapy · Evidence · Clinical trial

Introduction

Gastric cancer is the second leading cause of cancer death worldwide, and is the most frequently diagnosed malignancy in Japan, South America and Eastern Europe [1]. When gastric tumors are confined to local sites, complete resection is necessary to cure the cancer [2]. However, even when complete tumor removal is achieved, the cancer sometimes recurs after surgery [3]. Invisible micrometastatic tumor cells that exist beyond the extent of the surgical field at the time of surgery gradually grow to become a visible mass that can be detected on imaging studies or physical examinations. This is called a recurrence. Adjuvant chemotherapy aims to eradicate these micrometastatic tumor cells before and after curative surgery to improve the patient outcomes [4, 5]. The aim of this review is to clarify the standing position regarding neoadjuvant chemotherapy in Japan, where the standard treatment is postoperative adjuvant chemotherapy with S-1.

The term adjuvant chemotherapy is sometimes used to describe postoperative adjuvant chemotherapy in the narrow sense. Neoadjuvant chemotherapy refers to adjuvant chemotherapy that is administered preoperatively. In this report, we divided the category of adjuvant chemotherapy into postoperative adjuvant chemotherapy and neoadjuvant chemotherapy to make the meaning clear. This review summarizes the background, current status and future perspectives of neoadjuvant chemotherapy for gastric cancer.

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History of postoperative adjuvant chemotherapy

Many Phase III trials have been conducted to study the efficacy of postoperative adjuvant chemotherapy; however, most trials conducted before 2000 failed to show any survival benefit [6–9]. This can be explained, at least in part, by the low statistical power and/or poor patient compliance with chemotherapy in these studies. To compensate for the low statistical power, several investigators have reported the results of meta-analyses of these trials (Table 1). Hermans et al. [6] analyzed 11 randomized trials comparing surgery alone with postoperative adjuvant chemotherapy using a meta-analysis; however, they could not show any significant survival benefit of postoperative adjuvant chemotherapy. Earle et al. [7] examined 13 randomized trials conducted outside of Asia and demonstrated the presence of a small survival benefit of borderline statistical significance. They concluded that clinical trials should be continued to find and confirm effective adjuvant strategies [7]. Mari et al. [8] analyzed 21 randomized trials and showed similar results. Panzini et al. [9] reported the results of a meta-analysis of 17 randomized trials, and demonstrated a slight but significant survival advantage for postoperative adjuvant chemotherapy. Although several researchers have confirmed the presence of a slight benefit for postoperative adjuvant chemotherapy using meta-analyses, no pivotal Phase III trials had shown clear survival benefits.

During the late 1980s and 1990s, the Japan Clinical Oncology Group (JCOG) conducted several Phase III trials to compare the outcomes of surgery alone with those of postoperative adjuvant chemotherapy after D2 or more extensive gastrectomy (Table 2). JCOG 8801 compared the outcomes of surgery alone with those of treatment with MMC/5-FU and UFT for T1 or T2 disease; however, no significant differences were demonstrated due to an interaction between T1 and T2 [10]. The patients with T1 disease showed excellent survival rates regardless of the use of postoperative adjuvant chemotherapy, while those with T2 disease tended to show better survival rates with UFT treatment than with surgery alone. JCOG 9206-1 focused on patients with serosa-negative gastric cancer that corresponded to T2 disease [11]. This trial showed better survival outcomes in the postoperative adjuvant chemotherapy arm compared with the surgery alone arm; however, the difference did not reach statistical significance due to the small sample size. JCOG 9206-2 compared the outcomes of surgery alone with those of intensive chemotherapy

Table 1 Meta-analyses evaluating post-operative adjuvant chemotherapy

References	Journal (Reference)	No. of studies	No. of patients	Hazard ratio for death
Hermans [6]	JCO (#4)	11	2096	0.88 95 % CI 0.78–1.08
Earle [7]	EJC (#5)	13	1990	0.80 95 % CI 0.66–0.97
Mari [8]	Ann Oncol (#6)	21	3658	0.82 95 % CI 0.75–0.89
Panzini [9]	Tumori (#7)	17	3118	0.72 95 % CI 0.62–0.84

95 % CI 95 % confidence interval

Table 2 Results of JCOG phase III trial evaluating post-operative adjuvant chemotherapy

Study	Number of patients	Target	Test arm Control arm	Compliance/treatment completion (%)	Test arm (5y-OS) Control arm (5y-OS) %	Hazard ratio	*P* value
JCOG 8801	579	T1/T2	MMC/5FU → UFT	87 (individual dose intensity)	85.8	0.738	0.17
			Surgery alone		82.9		
JCOG 9206-1	252	Serosa-negative	FU + cytarabine	63	91.2	n.a.	0.14
			Surgery alone		86.1		
JCOG 9206-2	268	Serosa-positive	CDDP(ip) → 5FU/CDDP → UFT	39	62.0	0.992	0.48
			Surgery alone		60.9		

n.a. not available, *5y-OS* 5-year overall survival rate

Table 3 Pivotal phase III trials showing efficacy of post-operative adjuvant therapy

Study	Number of patients	Target	Test arm Control arm	Compliance/treatment completion (%)	Test arm (3y-OS) Control arm (3y-OS)	Hazard ratio	*P* value
INT-0116	556	IB-IVM0	Chemoradiation Surgery alone	64	50 % 41 %	0.74	0.005
ACTS-GC	1059	II/III	S-1 Surgery alone	66	80.1 % 70.1 %	0.68	0.003
CLASSIC	1035	II/III	Capecitabine + oxaliplatin Surgery alone	67	74 %/RFS 59 %/RFS	0.56	<0.0001

3y-OS 3-year overall survival, *RFS* relapse-free survival rate

consisting of intraperitoneal injection of CDDP, intravenous injection of 5-FU and CDDP and oral administration of UFT [12]. However, only 39 % of patients were able to complete the intensive chemotherapy. The survival results of the two arms were almost identical.

Since 2000, three pivotal Phase III trials have clarified the efficacy of postoperative adjuvant therapy (Table 3). The first trial, performed in the United States, compared the outcomes of surgery alone with those of postoperative adjuvant chemoradiation therapy [13]. A total of 556 patients were assigned to receive either surgery alone or chemoradiation consisting of treatment with 5-FU and leucovorin for 5 days, followed by 45 Gy of radiation combined with 5-FU and leucovorin on the first four and the last 3 days of radiotherapy, followed by two 5-day cycles of 5-FU and leucovorin. The overall survival rates were significantly higher in the chemoradiation arm than in the surgery alone arm. Based on the results of this study, postoperative chemoradiation became the standard treatment after curative gastrectomy in the United States. However, the quality of the surgery was not optimized in this study. Only 10 % of the patients received D2 dissection. Most patients underwent D0 (54 %) or D1 (36 %) resection. After a long debate [14], D2 surgery, which was originally established in Japan, was accepted as a standard surgery in Europe [15] and the USA [16]. The first report of a Dutch Phase III trial comparing the outcomes of D1 and D2 surgery showed that D2 surgery is risky and does not provide superior survival outcomes to D1 surgery [17]; however, the long-term observational report clearly demonstrated that D2 surgery reduces local recurrence after surgery and thereby contributes to survival [18].

Chemoradiation is a local therapy. It is quite reasonable to expect that postoperative adjuvant chemoradiation would be effective for patients who undergo D0 or D1 surgery, which are operations that do not adequately control cancer in local sites. In fact, chemoradiation was found to reduce the local and regional recurrence rates, but not distant recurrence [13]. Recently, a Phase III trial conducted in Korea (the Artist trial) did not show a survival benefit for postoperative chemoradiation therapy following D2 surgery [19].

The second pivotal Phase III trial clarified the efficacy of S-1 for stage II/III patients who underwent curative D2 surgery [20]. This nationwide study recruited over 1000 gastric cancer patients in Japan. Eighty mg/m^2 of S-1 was given after surgery for 1 year to patients in the chemotherapy arm. The 3-year overall survival rate was 80.1 % in the S-1 arm and 70.1 % in the surgery alone arm, which was a significant difference ($P = 0.003$). In the updated results of the ACTS-GC, the 5-year overall survival rate in the surgery alone arm and the S-1 arm was 71.3 and 84.2 % for stage II, 57.3 and 67.1 % for stage IIIA and 44.1 and 50.2 % for stage IIIB patients, respectively [21]. The hazard ratio (HR) was 0.509 in patients with stage II disease, 0.708 for stage IIIA and 0.791 for stage IIIB. Therefore, the effect of S-1 was higher for patients with stage II than stage III disease and higher for node-negative disease than node-positive disease. This was the first positive pivotal Phase III study to show that postoperative adjuvant chemotherapy is effective for treating gastric cancer after D2 surgery.

The third pivotal Phase III trial was conducted in Korea. In that trial, treatment with capecitabine and oxaliplatin significantly improved the disease-free survival (DFS) rate compared with surgery alone (CLASSIC trial) [22]. A total of 1035 patients were enrolled for 37 months in 37 centers in South Korea, China and Taiwan (nearly 90 % of the patients were treated in South Korea). The 3-year DFS rate was 74 % in the capecitabine and oxaliplatin arm and 59 % in the surgery alone arm. The hazard ratio (HR) was 0.56. The 3-year DFS rate in the surgery alone arm and the capecitabine and oxaliplatin arm was 71 and 85 % in stage II, 51 and 66 % in stage IIIA and 51 and 61 % in stage IIIB patients, respectively. The HR was relatively constant in stage II (0.55), IIIA (0.57) and IIIB (0.57), thus suggesting

that capecitabine and oxaliplatin are effective regardless of the stage. This was the first positive Phase III study to show that doublet combination chemotherapy including a platinum-based compound is effective for treating gastric cancer after D2 surgery.

The latter two pivotal Phase III trials support two approaches for postoperative adjuvant chemotherapy after D2 gastrectomy for resectable gastric cancer: S-1 for 1 year or capecitabine and oxaliplatin for 6 months [23]. The next treatment strategy for adjuvant chemotherapy in patients with gastric cancer should be considered based on these treatment approaches. The survival rates of patients with stage II disease reached over 80 % in both studies. Therefore, one goal should be the development of less toxic treatments. With capecitabine and oxaliplatin, the chemotherapy period is shorter and the treatment is more toxic than that observed with S-1. When considering the balance between the risks and efficacy of treatment, S-1 seems to be appropriate for patients with stage II disease. The JCOG has now launched a Phase III trial to compare the outcomes of treatment with S-1 for eight cycles (1 year) or four cycles (6 months) in patients with stage II disease. On the other hand, there remains some room for improvement in treating patients with stage III disease. More effective treatment is necessary to further improve the survival rates of stage III patients. Treatment with capecitabine and oxaliplatin, as used in the CLASSIC trial, seems attractive for treating patients with stage III disease.

Why should neoadjuvant chemotherapy be developed in Japan?

Single agent chemotherapy is not standard chemotherapy for treating advanced or recurrent gastric cancer [24]. In Japan, the SPIRITS Phase III trial showed that S-1, in addition to CDDP combination chemotherapy, significantly improved the survival rates of patients with advanced or recurrent gastric cancer compared with S-1 alone [25]. In Eastern Asia, another phase III trial was conducted to evaluate the efficacy of S-1 with docetaxel combination chemotherapy compared with S-1 alone (START trial) [26]. Although this trial could not show any significant superiority in the overall survival, this combination chemotherapy significantly prolonged the survival when the analysis was limited to the patients with non-measurable lesions, especially with peritoneal disease [27]. In the United States and Europe, triplet chemotherapy is the standard treatment for advanced or recurrent gastric cancer. The V325 Phase III trial demonstrated that combination chemotherapy with 5-FU, CDDP and docetaxel significantly prolonged the survival compared with doublet chemotherapy with 5-FU and CDDP [28]. Randomized trials conducted in European countries have demonstrated higher response rates and survival benefits with a regimen of epirubicin, cisplatin and infused fluorouracil (ECF) [29, 30]. The efficacy of this regimen has been confirmed in a meta-analysis [31]. Generally, chemotherapy regimens that have been proven to be effective for treating metastatic or recurrent gastric cancer have also been evaluated and proven to be effective in adjuvant settings for treating colon cancer. Therefore, doublet or triplet chemotherapy is a promising candidate for adjuvant chemotherapy that may help to further improve the survival rates.

Several Phase II studies have been conducted to evaluate the feasibility and safety of doublet chemotherapy after surgery. Kodera et al. [32] evaluated treatment with S-1 plus CDDP as postoperative adjuvant chemotherapy, and reported that the median relative dose intensity of S-1 and CDDP was only 37 and 40 %, respectively. They concluded that S-1 plus CDDP is, therefore, not feasible for evaluation in a further Phase III trial. Takahari et al. [33] also examined the feasibility and safety of S-1 plus CDDP after D2 gastrectomy. In the first protocol, CDDP was added to the first course just after surgery. However, grade 3 or 4 toxicities (anorexia and myelosuppression) were frequently observed, and most patients were not able to continue the treatment. The protocol was then amended so that CDDP was skipped in the first course. The treatment completion rates, which were defined as the completion rate of three rounds of CDDP, were 57 % before and 81 % after the protocol amendment. The authors concluded that treatment with S-1 plus CDDP is feasible when CDDP is not given during the first course just after surgery [33]. However, this study was conducted in several top Japanese hospitals, where the medical oncologists were highly accustomed to the management of CDDP and the adverse events involved. The generalizability of postoperative S-1 plus CDDP chemotherapy in Japan is, therefore, questionable, and as a result, combination chemotherapy with S-1 plus CDDP after surgery is not a generally accepted regimen.

Because S-1 plus docetaxel could show a survival benefit when the patients were limited to those with tumors associated with non-measurable lesions or peritoneal disease in the START phase III trial [26, 27]. S-1 plus docetaxel might be effective for micrometastatic tumors, especially for micrometastatic peritoneal tumors. Based on this study, a new phase III trial to examine the benefit of S-1 plus docetaxel is now planned in the postoperative adjuvant setting.

Differing from concurrent combination chemotherapy, sequential combination therapy after surgery is another candidate approach. Kobayashi et al. [34] conducted a Phase II study to evaluate the feasibility and safety of treatment with paclitaxel, followed by S-1, as postoperative adjuvant chemotherapy. They demonstrated that the

compliance at 6 months after surgery was 84 %, which is quite high. This regimen has also been tested in a large Phase III trial with a sample size of 1480 patients [35].

Therefore, three promising candidate regimens have been tested in clinical trials as postoperative adjuvant chemotherapy in Japan. The first one is concurrent combination chemotherapy with capecitabine and oxaliplatin, the second is concurrent combination chemotherapy with S-1 and docetaxel, and the last is sequential combination chemotherapy with paclitaxel and S-1. Treatments regimens with efficacy exceeding these regimens should be developed. However, it is questionable whether the administration of a more toxic combination regimen after gastrectomy is feasible or safe. As mentioned above, many Phase III trials failed to confirm any survival benefits for postoperative adjuvant chemotherapy, partially because of poor compliance. Concurrent doublet combination regimens including CDDP are not acceptable due to the high toxicity of the regimens. Although S-1 induces mild toxicities, the proportion of time to treatment failure at 12 months after surgery was only 65.8 % in the ACTS-GC [20].

Patients often suffer from a loss of appetite and decreased food intake after gastrectomy, which causes a loss of body weight and decreases their quality of life. These factors might influence the compliance with chemotherapy. We recently examined the risk factors for discontinuing S-1 after gastrectomy, and found weight loss after surgery to be a significant independent risk factor. Therefore, more toxic regimens administered after gastrectomy generally lack feasibility and safety, which is one reason to develop neoadjuvant chemotherapeutic strategies.

Another reason is the theoretical advantage of neoadjuvant chemotherapy. The aim of adjuvant chemotherapy is to eradicate micrometastatic tumor cells that cannot be resected during surgery. Without systemic chemotherapy, the micrometastatic tumor cells grow to form overt masses several months to years after surgery. Therefore, the presence of micrometastatic tumor cells determines the prognosis. However, no treatment for micrometastatic tumor cells is given until patients have recovered from surgery and postoperative chemotherapy is initiated. Meta-analyses have revealed that a longer interval between surgery and postoperative adjuvant chemotherapy is associated with worse survival rates in patients with colon cancer [36]. On the other hand, micrometastatic tumor cells are initially treated without delay in neoadjuvant chemotherapy regimens, which is another theoretical benefit of neoadjuvant chemotherapy.

Evidence supporting the benefits of neoadjuvant chemotherapy (Table 4)

Because many Phase III trials have failed to show any survival benefits for postoperative adjuvant chemotherapy, perioperative adjuvant chemotherapy was tested in a large Phase III trial (the MAGIC trial) in the UK [37]. This trial was designed to prove the superiority in overall survival rates of neoadjuvant and postoperative adjuvant chemotherapy combined with curative gastrectomy over surgery alone in clinically diagnosed stage II/III gastric cancer patients. Three courses of epirubicin, CDDP and 5-FU (ECF) were given before and after surgery. The estimated sample size to confirm the difference in 5-year survival rates of 33 % in the chemotherapy arm and 23 % in the surgery alone arm with an alpha error rate of 5 % and a statistical power of 90 % was calculated to be 500. A total of 503 patients were enrolled in this study between June 1994 and April 2002. The 5-year survival rate was 23.0 % in the surgery alone arm and 42.5 % in the perioperative chemotherapy arm, which was a statistically significant difference. The completion rate of the protocol treatment was only 41.6 %; however, the completion rate of neoadjuvant chemotherapy was over 80 %. Therefore, the survival benefits observed in the MAGIC trial seemed to be due to the effects of neoadjuvant chemotherapy. On the

Table 4 Results of phase III trials of neoadjuvant chemotherapy

Study	Number of patients	Target	Test arm Control arm	Compliance/ treatment completion (%)	Test arm (5y-OS) Control arm (5y-OS)	Hazard ratio	*P* value
MAGIC	506	II/III	ECFX3 → Surgery → ECFX3 Surgery alone	42	36 % 23 %	0.75	0.009
FNCLCC 94012	224	Resectable	CF X2-3 → surgery → CFX4-3 Surgery alone	48	38.0 % 24.0 %	0.69	0.020
EORTC 40954	144	III/IVM0	CFL → Surgery Surgery alone	63	72.7 %/2y 69.9 %/2y	0.84	0.466

5y-OS 5-year overall survival rate, *2y* 2-year overall survival rate

other hand, D2 gastrectomy was performed in 40.4 % of the patients in the surgery alone arm and in 42.5 % of the patients in the perioperative chemotherapy arm. Recurrence occurred less frequently at both local and distant sites in the perioperative chemotherapy arm (14.4 and 24.4 %, respectively) than in the surgery alone arm (20.6 and 36.8 %, respectively). The MAGIC trial therefore suggested that neoadjuvant chemotherapy is effective for treating distant sites even after D2 surgery.

Perioperative adjuvant chemotherapy has been tested in a Phase III trial (the FNCLCC/FFCD trial) in France [38]. This trial was designed to prove the superiority of neoadjuvant and postoperative adjuvant chemotherapy combined with curative gastrectomy over surgery alone for all resectable gastric cancers in terms of the overall survival rates. Three courses of CDDP and 5-FU (CF) were given before and after surgery. The estimated sample size to confirm a difference in the 5-year survival rates of 35 % in the chemotherapy arm and 20 % in the surgery alone arm with an alpha error of 5 % and a statistical power of 80 % was calculated to be 250. A total of 224 patients were enrolled in the study between October 1995 and December 2003. The 5-year survival rate was 24 % in the surgery alone arm and 38 % in the perioperative chemotherapy arm, which was a statistically significant difference. The completion rate of the protocol treatment was only 47.8 % (54/113), while that of the neoadjuvant chemotherapy was 97 % (109/113). Therefore, the survival benefits seemed to be due to the effects of neoadjuvant chemotherapy. On the other hand, the extent of dissection was not described in this trial. The rate of locoregional recurrence was not different between the groups; however, the rates of recurrence in distant sites and in concurrent locoregional and distant sites were reduced in the perioperative chemotherapy arm (30 and 12 %, respectively) compared to the surgery alone arm (38 and 18 %, respectively). The results of the FNCLCC/FFCD trial, therefore, also suggested that neoadjuvant chemotherapy seems to be effective for treating distant sites even after D2 surgery.

The most recent trial was the EORTC40954 Phase III trial conducted in Europe [39]. This trial was designed to prove the superiority of neoadjuvant chemotherapy combined with curative gastrectomy over surgery alone in the overall survival of clinically diagnosed stage III and IV patients with M0 gastric cancer. Two courses of CDDP, 5-FU and leucovorin (CFL) were given before surgery. Although the estimated sample size required to confirm the difference in a median survival of 24 months in the neoadjuvant chemotherapy arm and 17 months in the surgery alone arm with an alpha error of 5 % and a statistical power of 80 % was calculated to be 360, the study was terminated because of slow accrual when a total of 144 patients were enrolled between September 1999 and February 2004. When the median follow-up time was found to be 4.4 years in the neoadjuvant arm and 4.1 years in the surgery alone arm, the results were opened and reported. The overall survival rate did not reach the median survival time in either arm. Although the survival curve was slightly better in the neoadjuvant arm compared with the surgery alone arm, the difference did not reach statistical significance. The survival rate at 2 years was 72.7 % in the neoadjuvant arm and 69.9 % in the surgery alone arm. The completion rate of the protocol treatment was only 62.5 %, which is different from that observed in the MAGIC and FNCLCC/FFCD studies. On the other hand, D2 resection was performed in 95.7 % of the patients, which is an extremely high rate compared with that observed in the MAGIC trial.

The investigators indicated possible explanations for why the results of the EORTC40954 study were negative. These included the fact that there was low statistical power due to a small number of patients, a high rate of proximal gastric cancer (including junctional cancer) and/or a better than expected outcome after radical surgery alone due to the high quality of the surgeries. Moreover, the total courses of chemotherapy administered in each study were different: six in the MAGIC and FNCLCC/FFCD studies, and only two in the EORTC study. The rates of compliance with chemotherapy were also different: the compliance rate was higher than 80 % in the neoadjuvant part of the MAGIC and FNCLCC/FFCD studies and only 62.5 % in the EORTC study. These differences may have affected the results of the EORTC study.

So far, there have been no studies showing survival benefits for neoadjuvant chemotherapy by comparing neoadjuvant chemotherapy with surgery alone. However, it is impossible to conduct such a study at present, because the standard treatment worldwide includes surgery and adjuvant therapy. The standard treatment for patients with stage II or III gastric cancer is D2 surgery followed by adjuvant chemotherapy with S-1 in Japan [40], D2 surgery followed by adjuvant chemotherapy with capecitabine and oxaliplatin in Korea [22], D2 surgery followed by adjuvant chemotherapy with capecitabine and oxaliplatin in the USA [16] and D2 surgery combined with perioperative chemotherapy in Europe [15].

Pros and cons of neoadjuvant chemotherapy (Table 5)

We summarized the pros and cons of neoadjuvant chemotherapy by comparing postoperative adjuvant chemotherapy based on the MAGIC study. The rate of R0 resection was not improved in the MAGIC study. However, the number of patients who proceeded to the operation was decreased, so the R0 resection rate was high. Tumor

Table 5 Pros and cons of neoadjuvant and post-operative adjuvant chemotherapy

	Neoadjuvant chemotherapy	Postoperative adjuvant chemotherapy
%R0 resection	Substantially high	Low
	80.9 % (MAGIC)	66.4 % (MAGIC)
Regression	+	None
	T1:15.7 %/N0:31.1 % (MAGIC)	T1:8.3 %/N0:26.9 % (MAGIC)
Compliance	High	Low
	90.7 % (MAGIC)	75.9 % (MAGIC)
Toxicity	Same as metastatic disease	High GI toxicity
Initiation of chemotherapy	Same as metastatic disease	Decrease due to surgical morbidity
	97.1 % (MAGIC)	81.1 % (MAGIC)
Over-diagnosis	+	Accurate
	8.3 % of T1 (MAGIC)	–
Avoidance of unnecessary operation	+	None
	14.3 % (MAGIC)	–

regression due to the effects of chemotherapy and the avoidance of unnecessary surgery due to progression during chemotherapy contributed to the high R0 resection rate. The high compliance with chemotherapy due to low toxicities is another benefit of neoadjuvant chemotherapy compared with postoperative adjuvant chemotherapy. Generally, patients suffer from decreased food intake and a loss of appetite and body weight after gastrectomy, and such patients may be resistant to undergoing chemotherapy. Moreover, some patients cannot start chemotherapy after surgery due to surgical morbidity and mortality, which is one of the drawbacks to postoperative adjuvant chemotherapy. This is not the case with neoadjuvant chemotherapy, and the MAGIC trial clearly showed that the use of neoadjuvant chemotherapy did not increase the surgical morbidity or mortality. Nevertheless, the potential for over-diagnosis is a demerit of neoadjuvant chemotherapy. In the MAGIC trial, the target patients had clinical stage II disease, and all patients had clinical T2 tumors. However, 8.3 % of the patients had pathological T1 disease in the surgery alone arm.

Thus, neoadjuvant chemotherapy has several advantages over postoperative adjuvant chemotherapy. To maximize the efficacy of neoadjuvant chemotherapy, it is important to decrease the contamination of studies with patients who have T1 disease. Therefore, an accurate clinical diagnosis and objective criteria are important.

Current status of neoadjuvant chemotherapy in Japan

In Japan, the current standard treatment for stage II and III disease is D2 surgery and S-1 postoperative adjuvant chemotherapy. Neoadjuvant chemotherapy is an investigational treatment only permitted in clinical trials. So far, the JCOG has played a central role in the development of neoadjuvant chemotherapy.

When the JCOG conducted a trial around 2000, the candidates for neoadjuvant chemotherapy were carefully selected. At that time, the standard treatment was surgery alone, and chemotherapy regimens for advanced or recurrent disease other than 5-FU were under investigation. Extensive nodal disease was considered to be an indication for inclusion in a clinical trial. When patients with gastric cancer had para-aortic nodes, the 5-year survival rate was approximately 10 % at that time, even though complete resection was possible [41]. The other candidate patients were those with scirrhous gastric cancer, which had a 3-year survival rate of 20 % even with D2 dissection [42].

For patients with extensive nodal disease, two trials have been completed and one trial is ongoing (Table 6) [38, 39]. The JCOG-0001 Phase II study was conducted to evaluate the safety and efficacy of neoadjuvant chemotherapy consisting of two courses of CPT-11 and CDDP followed by D3 dissection [43]. The primary end point was to determine whether the lower 95 % confidence limit of the 3-year survival rate was greater than 15 %, and a sample size of 60 was calculated to ensure sufficient precision when the observed 3-year survival rate was 25–30 %. The study was terminated due to three treatment-related deaths (>5 %) out of 55 enrolled patients. However, the median overall survival time and the 3-year survival rate were 15 months (95 % CI 10–24 months) and 27 % (95 % CI 15–39 %), respectively, which met the primary endpoint for efficacy. For the same target, the JCOG-0405 study was conducted to evaluate the safety and efficacy of neoadjuvant chemotherapy consisting of two courses of S-1 and CDDP, followed by D3 dissection [44]. The primary end point was to determine whether the lower 95 % confidence limit of the proportion of patients who