gastric cancer, producing a higher resectability rate without any increase in morbidity rate. However, an interim analysis of the 2-year survival rate in 20 patients enrolled in the trial showed no improvement over the survival rate of the historical controls. Myelosuppression was the major cytotoxic effect of the FAMTX regimen, and grade 3 or 4 neutropenia was observed in 14 out of the 20 patients (70%). Eleven of these 14 patients required granulocyte colony-stimulating factor support. The overall response rate was 15% (3 PRs in 20 patients). Eighteen resected specimens showed only marginal histological effects (grades 0-Ib). For these reasons, Takahashi and co-workers discontinued the trial.

Because S-1 showed promising effects when used for neoadjuvant chemotherapy against scirrhous gastric cancer in a pilot study [9], we decided to conduct a phase II trial of S-1 to determine its beneficial effects on survival. Because of the difficulty in excluding patients with peritoneal dissemination by conventional diagnostic imaging procedures such as CT scan and the use of barium enema, we performed laparoscopic examination to identify and exclude patients with peritoneal dissemination.

At the time of starting the phase II trial, laparoscopic examination for cancer staging was still not a common procedure. Thus, we need to standardize this technique using a video for the quality control of the procedure. Regarding the historical controls, it was not possible to submit patients without peritoneal dissemination to laparoscopic examination, for the same reason. Data for previous patients with the same eligibility criteria and without peritoneal dissemination, confirmed by laparotomy, were collected from the participating institutions. Thus, in the present study, the control group was not identical to the study group.

Neoadjuvant chemotherapy using S-1 was safe and feasible when compared with other toxic combination chemotherapies. Only a few grade 3 and no grade 4 adverse reactions resulting from cytotoxicity were observed, and no specific morbidity and no increases in morbidity and mortality rates were seen when compared with the data in the historical controls.

Patients with positive cytological examination results were included in this phase II trial. This is the reason why we expected the S-1 neoadjuvant chemotherapy to produce negative cytological examination results. However, the results of the trial, in terms of cytological findings, were not very promising. Without considering the cytological examination results, it can be observed that although there was no significant difference in the curative resection rate between the study group and the historical control group, the curative resection rate in the study group was lower than the expected rate.

From the viewpoint of the pathological therapeutic effects of chemotherapy, S-1 neoadjuvant chemotherapy showed a much better therapeutic effect than FAMTX.

The survival rate of our study group showed a better curve than that of the historical controls; however, it did not reach the expected rate ($P = 0.245$). On the other hand, combination chemotherapy using S-1 and cisplatin (CDDP) showed a markedly high response rate (76%) in a phase II trial. Therefore, this combination can be considered more promising than S-1 monotherapy for neoadjuvant chemotherapy against scirrhous gastric cancer. The JCOG has also completed the accrual of patients evaluated in the phase II trial of neoadjuvant chemotherapy using the above S-1 and CDDP regimen for resectable scirrhous and more-than-8-cm giant type 3 gastric cancer. Because of the superiority of this regimen over S-1 monotherapy in terms of the response rate and pathological therapeutic effects, the JCOG group has already started a phase III trial to confirm the effectiveness of neoadjuvant chemotherapy using S-1 + CDDP as against extended surgery in patients with scirrhous or large type 3 gastric cancer.

In summary, neoadjuvant chemotherapy using S-1 against potentially resectable scirrhous gastric cancer appears feasible and effective; however, in the present phase II trial, the survival rate of the patients did not reach the expected rate. On the other hand, an S-1 + CDDP regimen is now being tested in a phase III trial by the JCOG group as a more promising neoadjuvant regimen.

Acknowledgments This study was supported by a Grant-in-Aid for Cancer Research and the Second Term Comprehensive Strategy for Cancer, both by the Ministry of Health, Labour and Welfare, Japan.

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CHALLENGES IN PERFORMING SURGICAL RANDOMIZED CONTROLLED TRIALS IN JAPAN

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SURGICAL TRIALS IN ONCOLOGY have gradually become more popular since the late 1980s. They remain a challenge, however, because of the large number of cases needed to provide adequate statistical power and the difficulty in maintaining quality control when treatment is provided by numerous participating surgeons.[1] The smaller the number of surgeons involved, the easier it is to ensure that high surgical standards are applied. However, as the number of surgeons decreases, the accrual period increases and the results become less generalizable. The optimum approach to such trials would be to use a group of surgeons with similar standards of safety and efficacy. The first section of this article lists the pitfalls of surgical trials based on the experience of the Dutch Gastric Cancer Study (DGCS), whereas the second section outlines the challenges faced by the Japan Clinical Oncology Group (JCOG) in its studies of gastric cancer and provides suggestions to surgeons who plan to carry out similar clinical trials.

LESSONS FROM THE DGCS

The author (M.S.) was asked to take on the role of instructor in the DGCS in 1989.[2] This study was one of the first multicenter randomized controlled trials (RCT) to evaluate 2 surgical procedures for cancer. Extended lymphadenectomy (D2) was compared with limited lymphadenectomy (D1) as treatments of curable gastric cancer. This study elucidated several critical problems in running surgical trials related to cancer treatment. Most of these issues have been pointed out in other articles.[3-6]

When to proceed to phase 3: ensuring patient safety. Specific training is required to perform any surgical procedure, which may be particularly the case with those aimed at cancer treatment.[7] Before starting the DGCS, only 1 of the Dutch surgeons had experience performing a D2 gastrectomy. Even in Japan, where both hospital and surgeon volumes are high, this procedure carries some risk of potentially fatal complications.[8] Retrospectively, a feasibility study to confirm the safety of this procedure when performed by Dutch surgeons on Dutch patients should have been carried out. Because prior to this study, no prospective phase 2 study had been conducted to evaluate the risk and safety of D2 dissection if performed by surgeons of little experience, we did not properly estimate the risk of 1 of the treatment arms and thus began a phase 3 trial without testing feasibility. Consequently, the hospital mortality of the D2 arm was 10%, which was more than double that of the D1 arm at 4%.[2] Similar or even worse postoperative mortality (14%) was observed in the Medical Research Council trials that compared D1 with D2, which was also carried out by surgeons with little experience in United Kingdom. These results are also the highest mortality rate reported in recent years among all cancer surgeries in high-volume hospitals, including esophageal and pancreatic cancers, which usually require more aggressive operative therapy than D2 gastrectomy.[9,10]

Defining procedural details. In this study, the details of both procedures were decided by a few surgeons, including the author (M.S.). The author had never observed operative performance of Dutch surgeons and, therefore, was unfamiliar with the standard techniques used for upper abdominal surgery in the Netherlands. Moreover, Dutch surgeons had no experience with D2 surgery. Thus, routine use of splenectomy and pancreatectomy in the D2 procedure was adopted in this trial, but in retrospect it was not the proper choice.[11] In multicenter trials on surgical procedures, a clear, detailed definition of each procedure is mandatory. The choice of a procedure must be based on the actual experience of the participants. Training via an instructional video or textbook is obviously insufficient. Ideally, all participating surgeons should engage in the process of defining the details of the procedure to be studied.

Quality control of treatment. If the quality of the operation is substandard, then the results should be carefully interpreted. In the words of U. Guller, "Garbage in, garbage out."[12] The greater the number of hospitals and surgeons involved in a trial, the wider the range of quality in surgical treatment that can be expected. This point is not an important issue in medical treatment, but it is a critical issue both in radiotherapy and in operative therapy. Quality control for radiotherapy may be easier than for surgical procedures. In the SWOG9008/INT0116 trial to evaluate postoperative chemoradiotherapy as adjuvant treatment for curable gastric cancer, a central review of the irradiation plan was carried out, and modification of the initial plan was performed in more than 30% of cases.[13] By managing quality control at a central level, trial leaders could minimize morbidity and anticipate the effect of radiotherapy. This trial proved the usefulness of postoperative adjuvant chemoradiotherapy, which is now the standard of care in the United States. This kind of quality control/assurance is not possible in an operation. As mentioned, only 1 of the participating

Accepted for publication March 13, 2009.

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Surgery 2009;145:598-602.

0039-6060/$ - see front matter

doi:10.1016/j.surg.2009.03.008

surgeons in the DGCS had ever carried out D2 gastrectomy before the study began. To provide a standard level of D2 dissection, 80 participating hospitals were divided into 8 regions where 1 or 2 specialists responsible for quality control always participated in D2 surgeries. The author (M.S.) remained in the Netherlands for the first 4 months of the study period to provide hands-on training to these individuals, who had had no prior experience with D2 surgery. Considering the complex nature of the procedure, this time frame was too short to afford adequate instruction, because only 33 patients were available for instruction of D2 surgery during this period. This allowed us to provide at maximum only 3 mentored exposures to D2 dissection for each quality controller. This example does emphasize the importance of quality control in surgical trials.[14]

In this trial, retrieved lymph nodes were examined in detail according to the protocol.[4] This method is useful in assessing the accuracy of lymphadenectomy. Although this method could improve the quality of operative therapy in hospitals where all dissected nodes are examined, thorough pathologic assessment of lymph nodes was seldom regarded as important in Dutch hospitals. In fact, the mean number of examined nodes from the specimens dissected by the author (M.S.) was counted as 31 if nodes were retrieved by Dutch pathologists and as 60 in other specimens from which all nodes were retrieved by the author (M.S.) himself.[15]

Regular monitoring and termination rules. As mentioned in the first section of this article, DGCS was started without any phase 2 studies to confirm feasibility, and no selection criteria limited hospital participation. Given this situation, rather strict termination rules should have been included in the protocol, based on hospital mortality rates, because of the uncertain safety of D2 gastrectomy performed by Dutch surgeons. A regular monitoring committee met to discuss problems in the trial, but much attention was not given to mortality issues. If an independent data and safety monitoring committee had existed, it could have recommended or ordered a temporary cease of accrual and could have changed the basic structure of the trial and minimized avoidable patient deaths. From an ethical point of view, more than double the risk of hospital mortality without certainty of an accompanying survival benefit is not acceptable in a randomized surgical study. If patients had been informed of the interim safety results, then it is doubtful that many would have accepted randomization.

Data handling and restriction of data access. An independent data center was implemented, but all data were accessible to investigators, and survival comparisons could have been carried out numerous times throughout the study period. In this study, there was no concept of multiplicity data analysis, and no planned interim analysis was required within the protocol. Survival analyses were carried out more than several times, the results of 2 of which were published without referring to the consumption of alpha error. Applying common sense with regard to statistical approaches should have prevented the problems in data analysis experienced in this study.

Postoperative care. The DGCS had many critical problems, as mentioned above, but it was still an important first step in this field. In particular, the heavy attention devoted to the quality control of an operation strongly affected studies planned afterward. However, no attention was given to the quality control of postoperative care in these patients; this issue that proved unexpectedly to be significantly related to the high hospital mortality rates that were observed. D2 surgery, which includes pancreaticosplenectomy, was expected to have high morbidity, but such high mortality after major complications was not anticipated. Hospital mortality after an anastomotic leak was greater than 40%, and that after pancreatic fistula with intra-abdominal abscess was 21%, whereas mortality rates after these events in a Japanese series in the 1980s were 14% and 3%, respectively.[16] Accumulation of experience was necessary to avoid postoperative hospital deaths after major complications. In the DGCS, the average number of D2 dissections per year was less than 2 per hospital; thus, gaining the postoperative management experience to avoid treatment related deaths was almost impossible. It has been suggested that Dutch patients might be much more fragile than those from Japan and that the high mortality rates observed might be caused by their underlying physical weakness. However, another RCT on the surgical treatment of esophagogastric junctional tumor (EGJT) performed by 2 specialized Dutch hospitals demonstrated much lower hospital mortality with a much higher incidence of potentially fatal major complications.[17] The only possible explanation is that the DGCS was carried out in 80 hospitals, which include peripheral general hospitals whose patient volume was low, whereas the EGJT study was performed in only 2 specialized centers. In the latter trial, each hospital had high volumes; thus, the requisite experience to manage potentially fatal complications and avoid treatment-related deaths was available.

CHALLENGES IN THE JCOG

Advantage of a cooperative group. In Japan, several cooperative groups exist, and the JCOG was the first and is the best organized of these. This organization has a strictly independent data center and 14 organ-specific groups. It also has a steering committee (headquarters) and several other functioning committees, such as an audit committee, data and safety monitoring committee, and protocol review committee. All aspects of a trial, especially safety aspects, are strictly monitored by several committees. Peer review by statisticians, medical oncologists, surgeons, or clinical research coordinators in various fields allows protocols to be clear, scientific, and ethical. All the data are controlled by the data center, and data sets cannot be accessed by researchers individually. Most trials include planned interim analyses, which are performed by statisticians that do not belong to the specific group conducting the trial. Survival results are shown only to the independent data and safety monitoring committee, which does not include any of the group's own researchers or statisticians. A lack of this type of organization was one of the many weak points of the DGCS.

Setting up phase 3 trials in the JCOG. In the JCOG, the first step in setting up a trial is to write a protocol concept. When the researchers in an organ-specific group agree to undertake a clinical trial, one of them writes a protocol concept to explain the background, methods, and feasibility of the study. With the help of the group's associated statistician, statistical aspects such as alpha, beta, and sample size are also discussed. A committee, which is composed of statisticians, medical oncologists, surgeons, and clinical research coordinators, peer reviews the protocol and then reports their evaluation along with any questions they might have. This report is discussed by the steering committee, and a vote is held to decide whether the study is worth performing in the JCOG. Any lack of safety information or lacking of experience of the participants involved in the study is usually pointed out, and the review committee sometimes recommends that the researchers carry out a feasibility study or a phase 2 study instead of proceeding immediately to phase 3. Especially in cases of surgical trials, hospital mortality should be maintained below 5% even with multidisciplinary treatment such as extended operative therapy after neoadjuvant chemotherapy. At the moment, a mortality rate higher than 5% is no longer acceptable in Japan for any cancer operation.

After approval by the steering committee, a full protocol is written by researchers together with coordinating physicians who are specialists at compiling protocols for clinical studies. This process takes a rather long time, especially in surgical trials, because the details of each surgical technique used in the study must be defined clearly and agreed on by all trial participants so as to minimize the variation in procedural implementation. Occasionally, selection of the participants is debated, especially in studies that require learning of new techniques, such as laparoscopic cancer surgery. The nature of the surgical technique also influences the decision of how to evaluate the results of the procedure performed in each case.

Actual trials in the Gastric Cancer Surgical Study Group (GCSSG) of the JCOG. In the GCSSG of the JCOG, 5 surgical trials have been conducted since 1995. The first trial, JCOG9501, was a phase 3 trial among 24 Japanese hospitals that compared D2 gastrectomy with superextended D3 gastrectomy, which is a D2 gastrectomy plus para-aortic nodal dissection, for T2b-T4 gastric cancer. Between July 1995 and April 2001, we randomized 523 patients intraoperatively to either the D2 arm (263 patients) or the D3 arm (260 patients). No adjuvant therapy was permitted until recurrence. The primary endpoint was overall survival. We paid careful attention to this initial surgical trial because of the experience of DGCS as previously mentioned. This trial selected surgeons who had experience with more than 100 gastrectomies with D2 dissection, or hospitals with an annual gastrectomy volume of more than 80 cases. During the study planning stages, all participating surgeons agreed to the technical details of both types of operations. In addition to reviewing the semiannual monitoring report, several participating surgeons presented videos of 1 or both procedures of arbitral patients to ensure uniformity of treatment and the procedures' technical details were discussed. To assess compliance with the specified type of lymphadenectomy, node retrieval in all regional nodal stations and number of dissected nodes in the para-aortic area were recorded on case report forms, which were also monitored. As a result, both surgical arms showed permissible complication rates and low hospital mortalities (0.8% in each arm).[8] Unexpectedly, no significant difference was observed in either overall survival or recurrence-free survival between the 2 groups. In conclusion, this first JCOG surgical phase 3 trial demonstrated that superextended D3 gastrectomy should not be used to treat this target population.[18]

In parallel with JCOG9501, another phase 3 trial was conducted to compare the effects of a left thoracoabdominal (LTA) approach with a abdominal-transhiatal (TH) approach in the treatment of gastric cancers with an esophageal invasion of 3 cm or less (corresponding mainly to tumors classified as Siewert type 2 or 3). Following a similar quality control procedure as JCOG9501, the JCOG9502 trial selected 27 specialized hospitals for participation. Only 3 patients died in hospital after LTA and none after TH. Morbidity was less favorable after LTA than after TH. Nevertheless, the survival of the LTA arm was diminished compared with the TH arm at the first interim analysis.[19] We therefore closed the accrual and opened the results according to the recommendation of the independent data and safety monitoring committee. Thus, the JCOG9501 and JCOG9502 trials demonstrated the ineffectiveness of more extensive surgeries and led to the establishment of standard surgeries in the field of gastric cancer.

Through the experience of these initial trials, other surgical trials were planned and are now ongoing in the GCSSG of the JCOG. JCOG0110 is a trial to evaluate the role of splenectomy in total gastrectomy for proximal gastric cancer in terms of survival benefit and postoperative morbidity.[20] Because this trial was designed in a noninferiority fashion, we have managed quality control more strictly than in previous trials, using a superiority-based approach so as not to affect the final results inappropriately. For example, the details of the planned surgical procedures were specified and described more clearly in the trial protocol before the study began. The number of dissected nodes in all stations was recorded on case report forms to be used for assessing the quality of operative therapy. We made a termination rule regarding hospital mortality in advance. If the number of deaths caused by surgical complications reached 10, the accrual would be stopped temporarily to wait for a judgment from the data and safety monitoring committee. The randomization to either gastrectomy with or without splenectomy was performed during operation after intraoperative confirmation of the eligibility criteria. Recruitment of the planned sample of 500 patients was accomplished in March 2009, after which all patients will be followed for 5 years.

We have also conducted a phase 2 trial of laparoscopy-assisted distal gastrectomy (LADG). Recently, this laparoscopic surgery technique has been established in specialized institutions. Although the technical difficulties of LADG have been solved gradually, some retrospective studies have reported that LADG is associated with a higher risk of surgical morbidities, such as anastomotic leak, stenosis, and pancreatic fistula, compared with open gastrectomy. The aim of the JCOG0703 trial is to evaluate the safety of LADG in clinical stage I gastric cancer. The primary endpoints are incidence of anastomotic leak and pancreatic fistula. If the incidence of these 2 postoperative complications is as low as expected (3% in total), then a subsequent phase 3 trial will be started to evaluate noninferiority of LADG compared with open gastrectomy in terms of long-term survival. Only surgeons with experience of more than 30 LADG and 30 open distal gastrectomies were allowed to participate in this trial. In addition to monitoring the number of dissected nodes in all stations with a case report form, we performed a central review of the surgical procedure by photographs of all patients and by videotaping of arbitrarily selected patients. This trial would have stopped accrual if treatment related deaths or life-threatening complications had reached 6.[21]

The latest JCOG phase 3 trial has just started with the international collaboration of the Korean Gastric Cancer Association. The prognosis of patients who suffer from incurable gastric cancer with hepatic or peritoneal metastases is poor. To investigate the role of gastrectomy in advanced gastric cancer with a single noncurable factor, 43 specialized hospitals (33 Japanese and 10 Korean) are conducting this REGATTA (JCOG0705) trial. Patients are randomized to either gastrectomy plus chemotherapy or to chemotherapy alone. The primary endpoint is overall survival, and the planned sample size is 330 with 2 years of follow-up after 4 years of accrual. The JCOG data and safety monitoring committee will independently perform the interim analysis and will consider stopping the trial early on behalf of both countries. Central monitoring is performed by the respective data center in each country to ensure data submission, patient eligibility, protocol compliance, safety, and on-schedule study progress. The monitoring reports are submitted to and reviewed by the respective data center independently every 6 months. The monitoring summary is exchanged between the 2 countries semiannually. Audits of the participating facilities are also carried out independently in each country, and brief summaries are exchanged. In this trial, if the number of treatment-related deaths reaches 9 in the chemotherapy-alone arm or 14 in the gastrectomy-plus-chemotherapy arm, the accrual will be stopped temporarily. Prior to its initiation, we had all expected significant difficulties in starting this international trial because of the many differences in medical culture and customs, as well as language, between Japan and Korea. Furthermore, most surgical trials are initiated by investigators without industrial sponsors, which requires them to obtain governmental or other competitive grants. Fortunately, the above challenges have been overcome, and the trial has been launched thanks to all the investigators' sincere efforts. Thus, the key to success in conducting high-quality surgical clinical trials is the investigators' enthusiasm and commitment to providing the best possible treatment to all future patients worldwide.

In conclusion, many issues in surgical oncology clinical trials are not relevant to medical oncology trials. If the treatment provided in surgical trials is not marked by the high quality afforded by specialists, the resulting benefits will not be appreciated by either patients or their providers. Establishing a cooperative group of specialists whose technical variance is minimal is therefore of paramount importance in performing meaningful clinical trials in surgical oncology.

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INVESTIGATIONS USING CLINICAL DATA REGISTRIES: OBSERVATIONAL STUDIES AND RISK ADJUSTMENT

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OUTCOMES RESEARCH has progressed a great deal in the past several years with the increasing availability of population-based data sources as well as other types of data registries. Also, the increasingly powerful and menu-driven statistical packages have made analyses of such data sets common, place, and have contributed to the increasing numbers of such publications. In this regard, however, there are a number of issues that an investigator needs to understand and address when performing such analyses. This article will review the following approaches to observational studies, with particular comments relevant to the use of clinical registry data:

- No risk adjustment
- Cohort study
- Case-control study
- Stratified study
- Regression-based risk adjustment
- Matching
- Propensity scores
- Instrumental variables

Following these observations, a few additional topics that are critical to the most common approaches will be briefly discussed:

- Sensitivity analysis
- Adjusting for exogenous and endogenous factors
- Regression to the mean
- Average treatment effect versus treatment effect on the treated
- The use of administrative data for risk adjustment

BACKGROUND: RANDOMIZED CONTROLLED TRIALS VERSUS OBSERVATIONAL STUDIES

The experiment is a critical element of the scientific method:

In the scientific method, an experiment (Latin: ex periri "of (or from) trying") is a set of observations performed in the context of solving a particular problem or question, to retain or falsify a hypothesis or research concerning phenomena. The experiment is a cornerstone in the empirical approach to acquiring deeper knowledge about the physical world.[1]

There are some critical and desirable features in the design of experiments. First, only one factor or treatment, referred to as the *experimental, treatment* or *independent variable,* should vary systematically across the experiment's groups. When this is true, the experiment is considered a *controlled experiment.* In controlled experiments, other factors that might also affect the outcome being studied do not vary systematically between groups. This method enables strong conclusions about the isolated effect of the experimental variable. A second major desirable feature in the design of experiments is for the outcome being studied (the *dependent variable*) to actually reflect an influence of the independent variable and for the measurement of that outcome to be possible without error or with describable error.

Accepted for publication March 3, 2009.

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Surgery 2009;145:602-10.

0039-6060/$ - see front matter

doi:10.1016/j.surg.2009.03.002

ANTICANCER RESEARCH *29*: 4689-4696 (2009)

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

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

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

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Key Words: S-1, cisplatin, advanced gastric cancer, preoperative chemotherapy, neoadjuvant chemotherapy.

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

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

Patients and Methods

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

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

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

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

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

Results

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

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

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

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

Table I. *Patient characteristics (N=120).*

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

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

Table II. *Patient characteristics of resected cases.*

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

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

Table III. *Response.*

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

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

Table IV. *Toxicity.*

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

response rate (ORR) was 62.5% (95% confidence interval (CI): 53.8-71.2%). There were 75 responders (one complete response (CR) and 74 partial responses (PR)), when the response to the primary lesion was disregarded. Response rate for regional/para-aortic lymph nodes, primary gastric tumor (assessed based on JGCA clinical criteria for response assessment of chemotherapy and radiotherapy), liver metastases and peritoneal metastases was 75.7% (56/74), 61.7% (74/120), 28.6% (2/7) and 23.8% (5/21), respectively. Twenty-five other patients (42.4%) had stable disease (SD), and only 2 patients had progressive disease (PD). Pathologic CR of the metastatic lymph nodes, including para-aortic lymph nodes, was confirmed after surgery in 4 patients. Of the 75 responders, residual tumor was completely resected in 51 (68.0%). Out of the 47 patients who underwent staging laparoscopy, 31 were found to have peritoneal metastasis; of these, complete remission of the peritoneal disease was confirmed at surgery in 9 (29.0%).

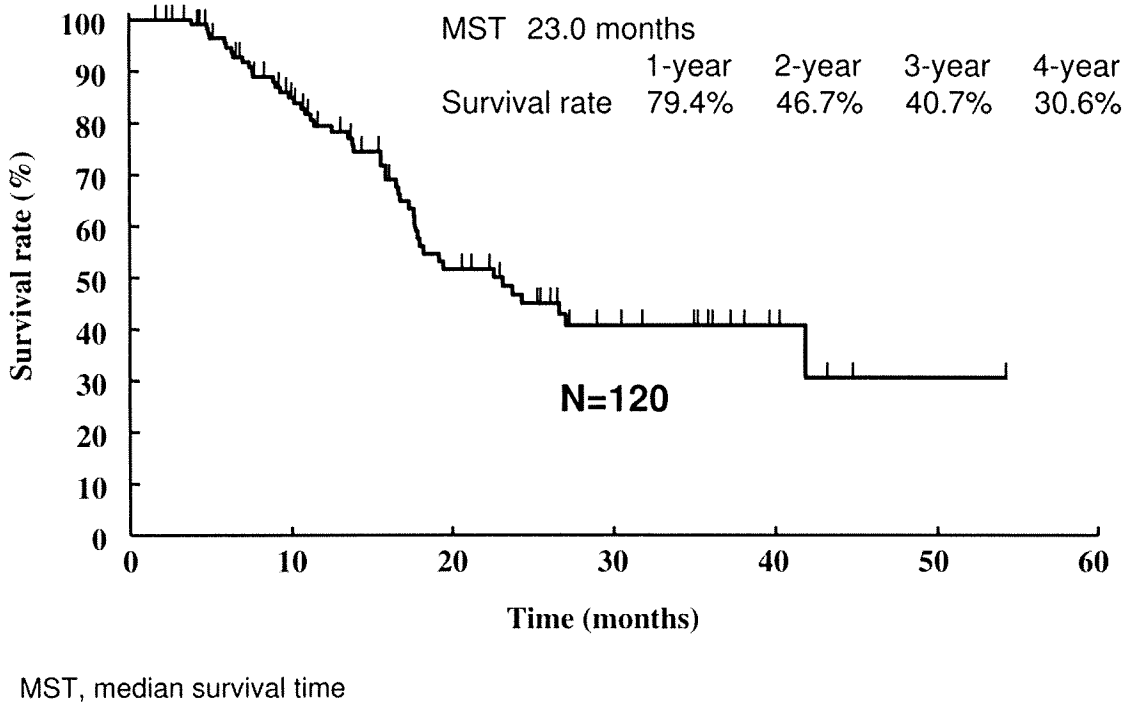

Figure 1. *Cumulative probability of overall survival as estimated by the Kaplan-Meier method in 120 patients. The median survival time was 23.0 months, and a 4-year survival rate was 30.6%.*

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

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

For all patients, response to chemotherapy, location of the tumor, resectability of the primary lesion, liver metastasis, and peritoneal metastasis were predictive of the overall survival (Table V). In the multivariate analysis, response to chemotherapy, peritoneal metastasis and hepatic metastasis were the only independently prognostic factors (Table VI). For the patients who were treated by gastrectomy, curability of surgery, response to the chemotherapy, hepatic metastasis, peritoneal metastasis, the extent of lymph node dissection, N category, and performance status were identified as significant prognostic determinants (Table VII). Of these, hepatic metastasis, curability of surgery, performance status and response to the chemotherapy were identified as independent prognostic factors (Table VIII).

Discussion

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

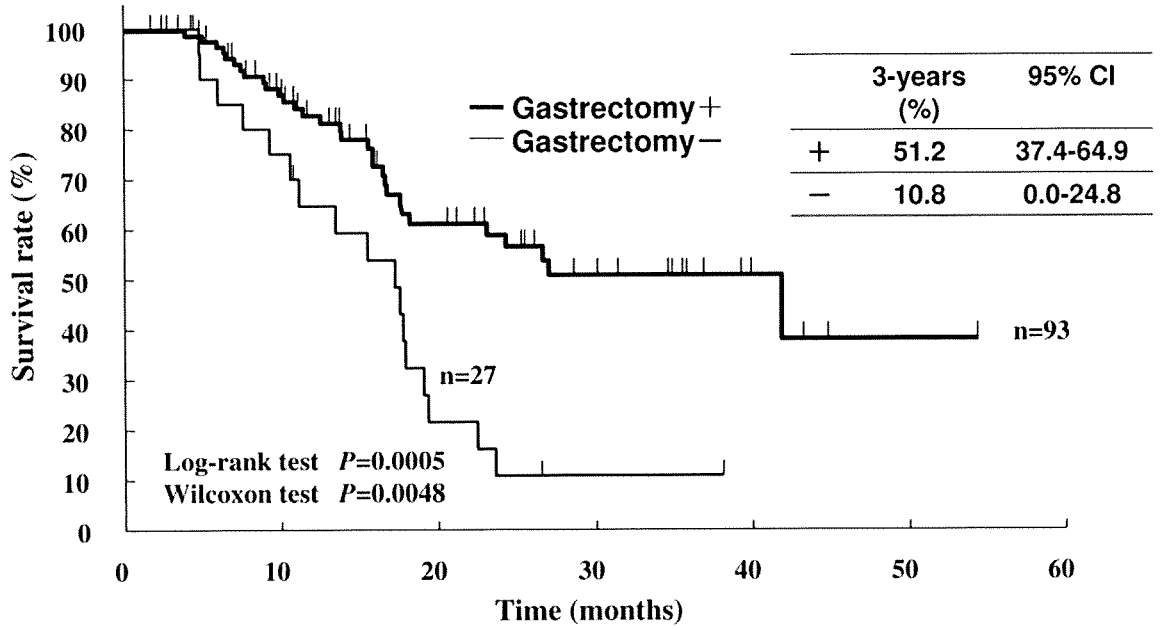

Figure 2. *Cumulative probability of survival in the gastrectomy group (93 patients) and the non-gastrectomy group (27 patients) as estimated by the Kaplan-Meier method. A 3-year survival rate of the former and the latter was 51.2% and 10.8%, respectively. There was a statistically significant difference.*

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

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

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

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

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

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

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

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

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

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

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

Response to the chemotherapy is undoubtedly a valuable parameter in deciding whether or not to proceed to surgery for metastatic cancer. When chemotherapy is performed in the neoadjuvant setting, however, cancer is usually resectable before the treatment. The response will then have to be evaluated even more cautiously and diligently to avoid delay in surgery when the cancer is not responding to the chemotherapy. When the tumor is not accompanied by distant metastasis or bulky lymphadenopathy, the primary lesion would be the only target for evaluating response. In addition, shrinkage of the primary may allow surgeons to avoid total gastrectomy in cases of advanced cancer of the distal or mid-portion of the stomach. Thus, the Authors insisted on assessing response in the primary lesion according to the Japanese criteria, although these lesions are not considered as measurable by the RECIST criteria. Marked response to the primary was observed in 61.7% of the patients.

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

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

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

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

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

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

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

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

Conclusion

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

Acknowledgements

We thank Professor Y. Kodera of the Department of Surgery II, Nagoya University Graduate School of Medicine for his critical review of this manuscript. This work was supported in part by as Grant-in-Aid from the Ministry of Health, Labour, and Welfare (Tokyo).

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Received July 27, 2009
Revised October 6, 2009
Accepted October 12, 2009

Original article

Phase II study of neoadjuvant chemotherapy and extended surgery for locally advanced gastric cancer

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Background: Locally advanced gastric cancer with extensive lymph node metastasis is usually considered unresectable and so treated by chemotherapy. This trial explored the safety and efficacy of preoperative chemotherapy followed by extended surgery in the management of locally advanced gastric adenocarcinoma.

Methods: Patients with gastric cancer with extensive lymph node metastasis received two or three 28-day cycles of induction chemotherapy with irinotecan (70 mg/m^2 on days 1 and 15) and cisplatin (80 mg/m^2 on day 1), and then underwent gastrectomy with curative intent with D2 plus para-aortic lymphadenectomy. Primary endpoints were 3-year overall survival and incidence of treatment-related death.

Results: The study was terminated because of three treatment-related deaths when 55 patients had been enrolled (mortality rate above 5 per cent). Two deaths were due to myelosuppression and one to postoperative complications. Clinical response and R0 resection rates were 55 and 65 per cent respectively. The pathological response rate was 15 per cent. Median overall survival was 14·6 months and the 3-year survival rate 27 per cent.

Conclusion: This multimodal treatment of locally advanced gastric cancer provides reasonable 3-year survival compared with historical data, but at a considerable cost in terms of morbidity and mortality.

Paper accepted 30 March 2009
Published online 30 July 2009 in Wiley InterScience (www.bjs.co.uk). **DOI:** 10.1002/bjs.6665

Introduction

Macroscopically complete tumour removal is a prerequisite to cure gastric cancer[1,2]. Japanese surgeons have explored the benefits and disadvantages of para-aortic nodal dissection for locally advanced tumours with nodal metastases[3–6]. The Japanese Gastric Cancer Association (JGCA) defines para-aortic lymph nodes as being regional lymph node stations (JGCA-N3)[7]. Tumours with bulky nodal metastases surrounding the coeliac artery and its branches (JGCA-bulky N2) are usually considered unresectable. The prognosis of patients with JGCA-N3 or JGCA-bulky N2 is extremely poor even when the entire tumour and lymph nodes can be resected with curative intent. Further, complete resection of these tumours often requires combined organ resection, such as distal pancreatectomy, resulting in major surgical complications[8]. Even after this surgery with curative intent, most tumours recur, suggesting that distant micrometastases were already present.

In contrast to the Japanese staging system, the tumour node metastasis (TNM) staging of the International Union Against Cancer (UICC) defines para-aortic metastases as

The Editors are satisfied that all authors have contributed significantly to this publication

distant metastases[9]. In Western countries, tumours with JGCA-N3 or JGCA-bulky N2 are therefore regarded as unresectable disease that warrants palliative chemotherapy. These patients rarely survive for more than 3 years when they receive chemotherapy alone or when surgery is followed by postoperative chemotherapy. To improve this dismal prognosis, a different strategy should be developed.

Preoperative chemotherapy has some theoretical benefits in these patients in comparison with postoperative chemotherapy. First, extended surgery can be performed easily and safely because the chemotherapy usually leads to shrinkage of lymph nodes, increasing the likelihood of R0 resection. Second, more intensive chemotherapy is possible with high compliance. Third, distant micrometastases can be treated early, before local therapy has begun. Recently, the effectiveness of a regimen of preoperative and postoperative epirubicin, cisplatin and infused fluorouracil for less advanced disease was suggested[10]. Combined chemotherapy using irinotecan hydrochloride plus cisplatin is also an attractive regimen for preoperative chemotherapy. In a phase II trial using this regimen in patients with metastatic gastric cancer, a response rate of 48 per cent and acceptable toxicity were reported[11].

The present study was conducted to evaluate the efficacy and safety of preoperative chemotherapy with irinotecan plus cisplatin followed by gastrectomy with D2 plus para-aortic nodal dissection for locally advanced gastric cancer with extensive lymph node metastases.

Methods

The study was conducted as a prospective multi-institutional phase II trial between 2000 and 2003 involving the 21 institutions of the Gastric Cancer Surgical Study Group of the Japan Clinical Oncology Group (JCOG). Patients with locally advanced gastric cancer presenting at their institution were considered for participation in the study. The absence of peritoneal dissemination was confirmed by laparoscopy before entry into the study.

Eligibility criteria

Eligibility criteria included: histologically proven gastric adenocarcinoma; para-aortic nodal metastases and/or bulky N2 cancers confirmed by contrast-enhanced computed tomography (CT) (definitions in *Fig. 1*); no metastases outside the para-aortic region, as confirmed by contrast-enhanced CT; no peritoneal or pleural effusion; no

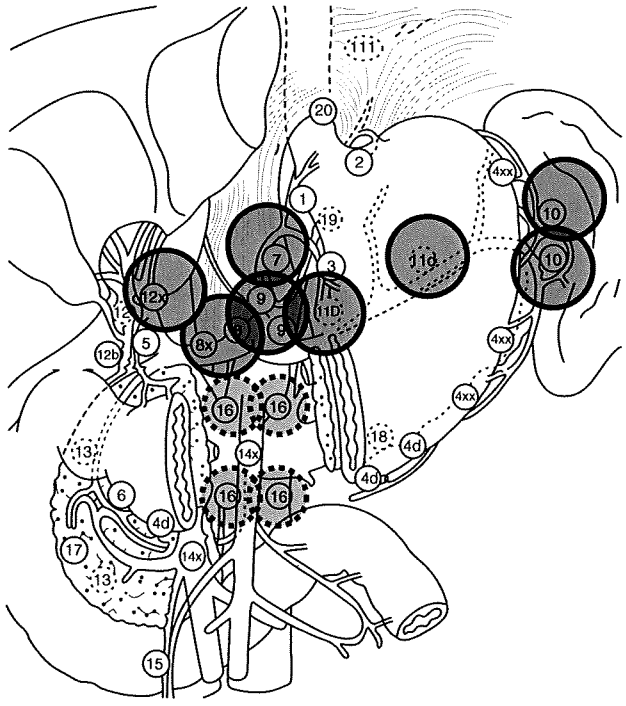

Fig. 1 Definitions of bulky N2 and para-aortic nodal metastases. Bulky N2 (in solid circles): at least one node of 3 cm or more in diameter, or at least three consecutive nodes each of diameter 1·5 cm or more, along the coeliac, splenic, common or proper hepatic arteries. Para-aortic nodes (in dashed circles): at least one node of 1 cm or more in diameter around the abdominal aorta

clinically apparent brain or bone metastases; no peritoneal metastases and negative cytology at laparoscopy; non-scirrhous type macroscopically; 20–70 years of age; Eastern Cooperative Oncology Group performance status 0 or 1; no previous chemotherapy or radiotherapy. In addition, patients had to have no signs of organ failure, as assessed by a white blood cell (WBC) count minimum of 4000/mm^3 and maximum of 12 000/mm^3, platelet count of 100 000/mm^3 or above, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) less than three times the upper limit of normal, total bilirubin 1·5 mg/dl or less, creatinine 1·2 mg/dl or less and creatinine clearance 60 ml/min or above, and haemoglobin 9·0 g/dl or more. There had to be no ischaemic change or ventricular arrhythmia on exercise electrocardiography, a forced expiratory volume in 1 s of 50 per cent or more, arterial partial pressure of oxygen (PaO_2) of 70 mmHg or above, and indocyanine green test in 15 min of 10 per cent or less in cases of liver dysfunction, negative serology for viral hepatitis and no past history of hepatitis. All patients gave written informed consent.

Exclusion criteria included: active gastrointestinal bleeding, infection, watery diarrhoea, synchronous or metachronous (within 10 years) malignancy other than carcinoma *in situ*, pregnancy or lactation, treatment with a major tranquillizer, lung fibrosis or interstitial pneumonitis, and bowel obstruction. Patients with allergic reactions to iodine were excluded because contrast-enhanced CT could not be performed. All patients were registered centrally at the JCOG Data Centre, where data management, central monitoring and statistical analysis were conducted. For quality assurance, a site visit audit was performed by the JCOG Audit Committee.

Preoperative chemotherapy

Irinotecan 70 mg/m^2 was administered on days 1 and 15 and cisplatin 80 mg/m^2 was given on day 1 as one course, repeated every 4 weeks[11]. If the patient had a WBC of 4000/mm^3 or less, platelet count of 10 000/mm^3 or lower, diarrhoea of grade 1 or above (increase of four or more stools per day over pretreatment), an episode of infection or abnormal serum creatinine concentration, administration of irinotecan and/or cisplatin was postponed until recovery. If recovery did not occur within 2 weeks, chemotherapy was stopped. On day 15 of each course, if the patient had an adverse event the second administration of irinotecan was postponed, and was not given if the adverse event was still observed on day 22. If the patient had haematological adverse events of grade 4 (haemoglobin level less than 6·5 g/dl, leucocyte count below 1000/mm^3, neutrophil count less than 500/mm^3, or platelet count below 25 000/mm^3), diarrhoea of grade 3 or higher (increase of more than seven stools per day or incontinence, or need for parenteral support for dehydration), or if the second administration of irinotecan was not given in the last course, the next dose of irinotecan was reduced to 60 mg/m^2. If the patient had a serum creatinine level of 1·2–1·5 mg/dl, the next dose of cisplatin was reduced to 60 mg/m^2. If serum creatinine was 1·5 mg/dl or above, initiation of the next course was delayed.

Some 7–13 days after the second administration of irinotecan in each course, resectability was evaluated based on CT findings by the Response Evaluation Criteria in Solid Tumours (RECIST)[12]. If curative resection was considered possible after the second course, the patient had surgery immediately. If curative resection was considered difficult, a further course of chemotherapy was added before surgery.

Surgery

Resection criteria included: R0 resection deemed possible by gastrectomy with D2 plus para-aortic nodal dissection, and no evidence of organ failure as assessed by a WBC count greater than 3000/mm^3 and less than 12 000/mm^3, platelet count above 100 000/mm^3, AST and ALT levels less than three times the upper limit of normal, total bilirubin less than 1·5 mg/dl, creatinine below 1·5 mg/dl and creatinine clearance above 50 ml/min, and PaO_2 greater than 70 mmHg. Eligible patients were operated on 3–6 weeks after chemotherapy.

After laparotomy, resectability was again evaluated and, if intraperitoneal wash cytology was negative, R0 resection was attempted by gastrectomy with D2 plus para-aortic nodal dissection, as described previously[13]. If necessary, D2 plus para-aortic nodal dissection was combined with splenectomy and/or distal pancreatectomy.

The treatment protocol was completed when a patient had received two or three courses of preoperative chemotherapy and had undergone R0 resection by gastrectomy with D2 plus para-aortic nodal dissection (*Fig. 2*). After completion of the protocol, no further treatment was given until tumour recurrence.

Quality control of surgery

During the recruitment period, participating surgeons and data centre representatives met three times per year to monitor the study. At each meeting, videos of various surgical procedures, including nodal dissection, were presented by several participating institutions,

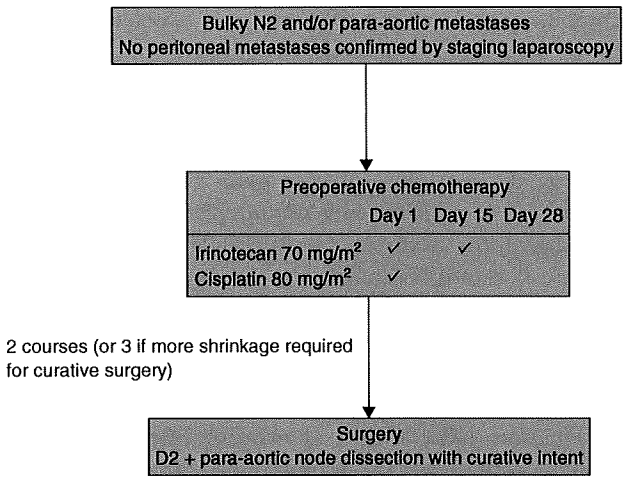

Fig. 2 Study outline

and technical details were discussed for critique. To assess compliance with lymphadenectomy, the number of dissected nodes was recorded.

Objectives and evaluation

Primary endpoints were overall survival and incidence of treatment-related death. Secondary endpoints were number of R0 resections, response to chemotherapy, chemotherapy-related toxicity and surgical complications. Clinical response was evaluated by RECIST[12], based on CT with a central review. Surgical specimens were evaluated pathologically and graded according to the proportion of tumour affected by degeneration or necrosis[14]: grade 0, no part of tumour affected; grade 1a, less than one-third affected; grade 1b, between one-third and two-thirds affected; grade 2, between two-thirds and entire tumour affected; and grade 3, no residual tumour. A pathological response was defined as one-third or more of the tumour affected (grade 1b, 2 or 3). Adverse events during chemotherapy were evaluated by the National Cancer Institute – Common Toxicity Criteria version 2.0[15].

Statistical analysis

For sample size calculation, treatment was considered effective if the lower limit of the 95 per cent confidence interval (c.i.) for 3-year survival exceeded 15 per cent. In terms of feasibility and efficiency, sample size was determined as 60 with a 3-year entry and 3-year follow-up period. In this setting, the exact binomial lower confidence limit for a 3-year overall survival rate of 30 per cent (18 of 60) was 18·9 per cent and that for 25 per cent (15 of 60) was 14·8 per cent. This was considered sufficiently precise to make inferences based on 3-year survival. Hence, the sample size was calculated as 60.

The survival curve was estimated using the Kaplan–Meier method; 95 per cent c.i. were calculated with the Greenwood formula[16]. Treatment was considered safe if point estimates of treatment-related death did not exceed 5 per cent. The stopping rule for safety was prespecified so that the study would be terminated when treatment-related death had been observed in three patients (treatment-related death exceeding 5 per cent). Statistical analysis was performed with SAS® version 8.2 (SAS Institute, Cary, North Carolina, USA). This phase II trial was approved by the JCOG Protocol Review Committee and institutional review board of each institution involved.

Results

Between August 2000 and May 2003, 55 patients were entered into the study and underwent preoperative chemotherapy. All patients were followed for more than 3 years after registration. When 55 patients had been registered, three were judged as treatment-related deaths by the JCOG data and safety monitoring committee, and the study was terminated according to the stopping rules. Thus, the treatment-related death rate was 5 (95 per cent c.i. 1 to 15) per cent. *Table 1* shows patient demographics and tumour characteristics. A flow diagram from chemotherapy to surgery is shown in *Fig. 3*. The clinical response rate for all eligible patients was 55 (95 per cent c.i. 41 to 68) per cent (30 of 55 patients) (*Fig. 3*).

Table 1 Demographics and tumour characteristics in 55 eligible patients

Median (range) age (years)	63 (46–70)
Sex ratio (M : F)	42 : 13
ECOG performance status	
0	47
1	8
Histology	
Differentiated	30
Undifferentiated	25
Nodal status	
Para-aortic nodes and bulky N2	19
Only para-aortic nodes	11
Only bulky N2	25

ECOG, Eastern Cooperative Oncology Group.

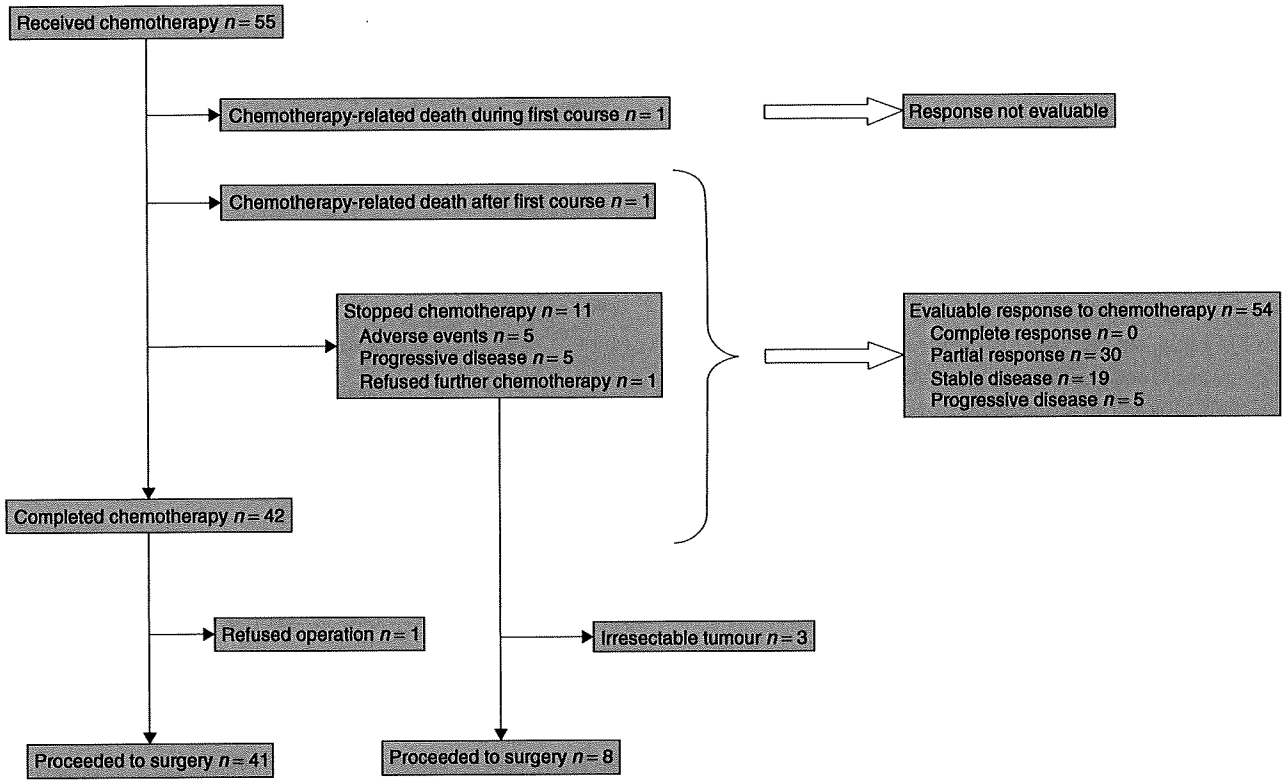

Fig. 3 Flow diagram from chemotherapy to surgery in 55 eligible patients

Table 2 Details of 49 patients who underwent surgery

	No. of patients
Peritoneal cytology	
Negative	45
Positive	4
Type of resection	
Total gastrectomy	32
Distal gastrectomy	15
Bypass	1
Exploratory laparotomy	1
Dissection of nodes along splenic artery	
With splenectomy and distal pancreatectomy	14
With splenectomy	16
Without splenectomy	13
No nodal dissection	6†
Operating time (min)*	370 (40–930)
Blood loss (ml)*	1050 (0–5650)
Blood transfusion	34
No. of para-aortic nodes dissected*	26 (0–86)
No. of nodes dissected*	87 (45–179)

*Values are median (range). †Exploratory laparotomy in one patient, bypass in one, palliative resection in one and non-curative resection in three patients.

Table 3 Pathological findings in resected patients

	No. of patients (n = 47)
Depth of tumour invasion	
T1	3
T2	18
T3	19
T4	6
Unknown	1*
JGCA, nodal status	
N0	1
N1	7
N2	9
N3	30
JGCA, pathological response	
Grade 0	6
Grade 1a	33
Grade 1b	2
Grade 2	5
Grade 3	1

*Not evaluable as no residual cancer cells. JGCA, Japanese Gastric Cancer Association.