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Phase II Study of Sequential Methotrexate and 5-Fluorouracil Chemotherapy Against Peritoneally Disseminated Gastric Cancer with Malignant Ascites: a Report from the Gastrointestinal Oncology Study Group of the Japan Clinical Oncology Group, JCOG 9603 Trial

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Background: The efficacy of systemic chemotherapy against peritoneal dissemination from advanced gastric cancer (AGC) remains unclear, because the peritoneal dissemination was not defined as a measurable lesion in conventional phase II studies. In this study, we evaluated the efficacy and toxicity of sequential MTX and 5FU therapy (MF) in chemotherapy-naive patients with AGC accompanied by malignant ascites in a phase II setting.
Methods: The treatment schedule comprised weekly administration of MTX (100 mg/m^2, i.v. bolus) followed by 5FU (600 mg/m^2, i.v. bolus) with a 3 h interval. Leucovorin rescue (10 mg/m^2 every 6 h, for a total of six times) was commenced 24 h after MTX administration.
Results: Thirty-seven chemotherapy-naive patients with AGC presenting with malignant ascites were enrolled in this trial. The median age was 60 years (range, 25–74 years) and most patients (86%) had a performance status of 0–1. In total, 355 administrations of the sequential MTX/5FU therapy were performed. Major toxicity consisted of myelosuppression and gastrointestinal toxicity. Grade 4 neutropenia occurred in 10.8% of the patients. The overall objective response rate was 5.7% (two partial responses in 35 patients; 95% confidence interval: 0.7–19.2%). However, the response rate of ascites was 35.1% (complete disappearance in three patients and apparent decrease in 10 patients; 95% confidence interval: 20.2–52.5%).
Conclusions: Sequential MTX/5FU therapy is effective against AGC with malignant ascites with acceptable toxicity and warrants further investigations in a phase III setting.

Key words: sequential MTX/5FU chemotherapy – gastric cancer, peritoneal dissemination – ascites – clinical trial

INTRODUCTION

Despite a declining incidence in many industrial countries, gastric cancer remains one of the most common malignancies globally. Although this tumor is potentially curable with surgery when diagnosed at an early stage, the prognosis for patients with unresectable or metastatic disease is very poor, with a median survival of 3–4 months when they receive the best supportive care without palliative surgery or chemotherapy (1–3). Gastric cancer can progress to systemic disease through various routes such as direct invasion or lymphatic or vascular spread. Peritoneal dissemination, i.e. peritoneal carcinomatosis, which occurs mainly as a result of direct invasion and/or lymphatic spread, is very common in advanced gastric cancer and is considered an incurable disease state (4). Peritoneal dissemination may cause serious complications, such as

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intestinal obstruction, massive ascites and hydronephrosis associated with the clinical presentation of abdominal pain and fullness, vomiting, constipation, malnutrition and renal dysfunction. From the clinical point of view, palliative management of those complications warrants special considerations and represents a therapeutic challenge in oncology (5,6). Although the major treatment option for unresectable or metastatic gastric cancer is systemic chemotherapy, this strategy has been generally believed to have little effect on peritoneal dissemination, because the drugs could not be delivered sufficiently through the peritoneum–plasma barrier to the disseminated tumor cells (7). However, the efficacy of systemic chemotherapy against peritoneal dissemination from gastric cancer remains unclear, because peritoneal dissemination was not defined as a measurable lesion in conventional phase II studies and therefore few reports are available about the efficacy of systemic chemotherapy against peritoneal dissemination. 5-Fluorouracil (5FU) remains the mainstay for chemotherapy against gastric cancer and a variety of drugs have been tested as modulators to increase its chemotherapeutic efficacy. The modulators that have been most widely used in clinical practice against gastrointestinal tract cancers are folinic acid (leucovorin) and methotrexate (MTX) (8,9). MTX enhances 5FU cytotoxicity via DNA and/or RNA synthesis inhibition when the two drugs are administered in sequence, with 5FU administered a few hours after MTX (10,11). A meta-analysis of randomized trials of sequential MTX/5FU therapy revealed a higher response rate than for single agent bolus 5FU in colorectal cancer (12). The toxicity of these sequential MTX/5FU regimens was comparable to that of 5FU alone (i.e. vomiting, stomatitis, diarrhea and leukopenia). The sequential MTX/5FU therapy was found in phase II trials for advanced gastric cancer to have antitumor activity against advanced gastric cancer (13,14). A Japanese phase II trial of sequential MTX/5FU therapy against advanced gastric cancer demonstrated that low- and intermediate-dose MTX regimens achieved response rates of 23% (13 PRs/56 patients) and 41% (15 PRs/37 patients), respectively (15). Sequential MTX/5FU therapy is widely used as one of the standard treatment regimens for patients with unresectable or metastatic gastric cancer at present in Japan. Konishi et al. reported that sequential MTX/5FU therapy was effective in patients with peritoneal dissemination with a response rate of 23% (6/26) and that ascites disappeared in eight of 16 patients (50%) treated with this therapy (16). Those findings suggest that sequential MTX/5FU might be effective in advanced gastric cancer with peritoneal dissemination.

The objective of this study was to evaluate the efficacy and toxicity of sequential MTX/5FU chemotherapy in advanced gastric cancer with malignant ascites in order to determine whether this regimen is worthy of further investigation in a phase III trial for the treatment of patients with peritoneal dissemination from advanced gastric cancer. The primary endpoints planned for this study were tumor response rate and response rate in ascites. Secondary endpoints were overall survival and toxicity. To our knowledge, there has been no prior study that evaluated the efficacy and toxicity of systemic chemotherapy in a phase II setting in patients with advanced gastric cancer who have peritoneal dissemination with malignant ascites.

SUBJECTS AND METHODS

Eligibility

Patients enrolled in this study were required to fulfill the following eligibility criteria: (1) histologically confirmed gastric cancer; (2) unresectable or recurrent disease; (3) peritoneal dissemination with cytologically confirmed malignant ascites evaluable by CT scan or ultrasonography; (4) measurable or evaluable disease; (5) age 20–75 years; (6) performance status (PS) ≤2 on Eastern Cooperative Oncology Group (ECOG) scale; (7) no prior chemotherapy with the exception of one adjuvant chemotherapy; (8) adequate bone marrow function (WBC ≥4000/mm^3 and platelets ≥100 000/mm^3) (9) adequate liver function (serum bilirubin level ≤2.0 mg/dl and serum transaminase level ≤2.5-fold the upper limit of normal; (10) adequate renal function (serum creatinine and blood urea nitrogen within the upper limit of normal; (11) serum albumin ≥2.6 g/dl; (12) normal ECG; (13) currently hospitalized; (14) life expectancy at least 8 weeks; (15) written informed consent. Patients with active bleeding from the gastrointestinal tract, other active synchronous carcinoma, central nerve metastasis or concurrent uncontrolled medical illness and pregnant or lactating women were excluded. Patients with massive ascites that required drainage for the relief of symptoms were also excluded. The study protocol was approved by the JCOG Clinical Trial Review Committee and by the institutional review board of each participating center.

Treatment Plan

The treatment schedule comprised weekly administration of MTX (100 mg/m^2, i.v. bolus) followed by 5FU (600 mg/m^2, i.v. bolus) with a 3 h interval. Leucovorin rescue (10 mg/m^2 orally or i.v. every 6 h, six times) was commenced 24 h after MTX administration. To prevent toxicity from MTX, acetazolamide (250 mg) was given intravenously immediately after the infusion of MTX and sodium bicarbonate (33.3 mequiv.) added to 500 ml of electrolyte solution was administered by drip infusion for urine alkalinization during the 3 h interval between the administration of MTX and 5FU. The plasma level of MTX was monitored 24 h after MTX administration and leucovorin rescue at 10 mg/m^2 was administered every 6 h until the plasma level of MTX was $<1 \times 10^{-6}$ mol/l. At the time of each administration, patients were required to fulfill the following criteria: leukocyte count ≥3000/ mm^3; platelet count ≥75 000/ mm^3; adequate liver and renal function as eligibility criteria; PS 0–2; and absence of toxicity grade 2 or greater. The treatment was repeated unless disease progression or severe toxicity was observed. The treatment was terminated when the ascites did

Table 1. Patients' characteristics

Characteristic	Total ($n = 37$)
Gender	
Male	21
Female	16
Age (years)	
Median	60
Range	25–74
ECOG performance status score	
0	8
1	24
2	5
Histological type	
Intestinal type	
Well-differentiated tubular adenocarcinoma	4
Moderately differentiated tubular adenocarcinoma	7
Papillary adenocarcinoma	1
Diffuse type	
Poorly differentiated adenocarcinoma	6
Mucinous adenocarcinoma	2
Signet-ring cell carcinoma	17
Macroscopic type of primary tumor	
Scirrhous type	21
Non-scirrhous type	16
Metastatic sites	
Lymph nodes	25
Liver	7
Krukenberg's tumor	2
Douglas's metastasis	1
Lung	2
Bone	1
Pleural effusion	4

not improve within 8 weeks or when toxicity did not disappear within 6 weeks.

Response and Toxicity Evaluation

Tumor response was assessed by CT scan or ultrasonography of the target lesions every 4 weeks after the first administration of MTX. Complete response (CR), partial response (PR), no change (NC) and progressive disease (PD) were defined according to the response assessment criteria proposed by the Japanese Research Society for Gastric Cancer (17). The response in ascites was evaluated by abdominal CT scan or ultrasonography based on the following specific criteria used in this study: (1) disappearance of ascites – disappearance of ascites visualized by CT scan or ultrasonography for at least 4 weeks; (2) decrease of ascites – apparent decrease of ascites visualized by CT scan or ultrasonography for at least 4 weeks; (3) no response of ascites – no change of ascites volume visualized by CT scan or ultrasonography. The data for tumor response in all responders was confirmed by an extramural review. The toxicity was evaluated according to the JCOG common toxicity criteria (18).

Statistical Analysis

The sample size was determined based on the precision of the estimates. The efficacy for malignant ascites was expected to be 30%. Fifty subjects and an observed efficacy of 30% would provide a 95% confidence interval of 17.9–44.6% or width of 26.7%. The expected accrual period was 1.5 years. Interim analysis was planned to test for inefficacy of the treatment by examining whether a 90% upper confidence bound of efficacy would exceed 25% for first 20–25 patients. The overall survival was calculated for the period from the date of registration to the date of death. Overall survival was calculated by the Kaplan–Meier method and confidence intervals were calculated based on Greenwood's formula.

RESULTS

Patient Population and Study Treatment

Between February 1997 and October 1999, 37 patients were enrolled in this trial from nine out of 13 participating institutions. Although this study was originally planned as a phase II study in which 50 patients would be enrolled within 1.5 years of the start of the study, the patient enrollment was delayed and was finally terminated before the projected number of patients had been achieved based on the decision of the JCOG monitoring committee that the evaluation of efficacy and toxicity was possible even with only 37 enrolled patients. Table 1 lists the demographic data, baseline disease and pretreatment characteristics of all patients. Twenty-one males and 16 females were registered as receiving first-line chemotherapy. The median age of the patients was 60 years (range, 25–74 years) and the majority of the patients (86%) had a good performance status of 0–1. Twenty-one patients (57%) had macroscopically scirrhous-type advanced gastric cancer. Twenty-five patients had histologically diffuse types (six poorly differentiated adenocarcinoma, two mucinous carcinoma and 17 signet-ring cell carcinoma). Two patients had undergone surgery prior to enrollment in this trial (one palliative total gastrectomy and the other exploratory laparotomy resulting in no resection). One patient suffered from hemilateral hydronephrosis due to peritoneal dissemination with normal range of renal function tests.

In total, 355 administrations of the sequential MTX/5FU therapy were performed in 37 patients. The median number of administrations was eight (range, 1–42). Twenty-nine of 37 enrolled patients (78%) received at least four administrations of the sequential MTX/5FU therapy. All patients were assessable for toxicity and response of ascites to chemotherapy. Thirty-five patients were assessable for objective tumor

Table 2. Toxicity profiles

Toxicity	JCOG grade					Grade 4 (%)
	0	1	2	3	4	
Hematological toxicity						
Leukopenia	11	13	7	4	2	5.4
Neutropenia	17	5	5	6	4	10.8
Anemia	7	6	15	9	–	–
Thrombocytopenia	32	3	1	1	0	0
Non-hematological toxicity						
Nausea/vomiting	13	14	10	0	–	–
Diarrhea	25	4	6	2	0	0
Stomatitis	30	7	0	0	0	0
Alopecia	35	2	0	–	–	–
Allergic reaction	36	1	0	0	0	0
Fever	18	10	9	0	0	0
Peripheral neuropathy	36	1	0	0	–	–
Total bilirubin	20	–	8	8	1	2.7
AST	16	16	5	0	0	0
ALT	16	16	5	0	0	0
Alkaline phosphatase	16	17	2	2	0	0
Creatinine	33	2	0	2	0	0
Hyponatremia	12	17	7	0	1	2.7
Hypokalemia	21	12	4	0	0	0

response to chemotherapy. The most frequent reason for treatment termination was disease progression (27 patients, 73%). Other reasons for treatment termination were no response after 8 weeks from initiation of treatment in two, patient refusal in two, severe toxicity in two, death in three (one due to disease progression and two treatment-related) and medical judgment by the investigators in one.

Toxicity

The toxicity observed in the study period is summarized in Table 2. The major toxicity was myelosuppression and gastrointestinal toxicity. Grades 3 and 4 neutropenia occurred in 16 and 11% of the patients, respectively. Severe thrombocytopenia was infrequent. The incidence of grade 3 diarrhea was 5%. Mild nausea and vomiting (grades 1 and 2) were frequently experienced (65%). An increase in total bilirubin of grade 4 was observed in one patient (2.7%) and was diagnosed as obstructive jaundice caused by the development of lymphadenopathy from the primary disease. An increase in total bilirubin grade 3 was observed in eight patients, three cases of which were judged to be treatment-related. An increase in serum creatinine grade 3 was observed in two patients (5.4%). One patient experienced grade 4 hyponatremia due to loss of oral intake associated with primary disease. Early death, which was defined as death within 30 days from the last administration of anti-cancer drugs, occurred in five patients. The causal relationship between the death and the study treatment was 'unlikely' in three of those five patients. However, the remaining two deaths were assessed to be treatment-related. One patient died of severe neutropenia and rapidly progressive disseminated intravascular coagulation (DIC), which was complicated with respiratory dysfunction, and the other patient died of progressive neutropenic sepsis.

Efficacy

The efficacy-related data are summarized in Table 3. Only two of 35 response-assessable patients achieved objective partial response (response rate 5.7%; 95% confidence interval: 0.7–19.2%). However, in terms of the response of ascites, three disappearances and 10 decreases of ascites were obtained (response rate 35.1%; 95% confidence interval: 20.2–52.5%). The median duration of response of ascites was 103 days with a range of 52–337 days. The median survival time of all patients was 155 days (95% confidence interval: 131–225 days) and the 1 year survival rate was 16.2% (95% confidence interval: 4.3–28.1%).

DISCUSSION

Although unresectable or metastatic gastric cancer is potentially incurable, there is significant evidence that adding systemic chemotherapy to the best supportive care could provide benefits in survival and quality of life as compared with best supportive care alone (1–3). However, it has been difficult to assess which of many available regimens is the most effective, although several regimens have been tested in randomized controlled trials. Some randomized trials failed to demonstrate the superiority of 5FU-based combination regimens as compared with 5FU-monotherapy (19–21). A recent randomized controlled trial showed that three commonly used combination regimens, 5FU/adriamycin/MTX (FAMTX), 5FU/cisplatin (FP) and etoposide/leucovorin/5FU (ELF), have only modest activity and that there were no significant differences in overall survival among these regimens (22). More recently, infusional 5FU in combination with cisplatin and epirubicin (ECF) showed significant superiority over FAMTX in terms of response rate, quality of life and survival, suggesting that the ECF could be a new standard treatment for future clinical trials (23). However, regarding the median survival time in those large-scale trials, there was little substantial difference among the various regimens. Therefore, in general, 5FU-based or cisplatin-based combinations are widely accepted as a possible standard therapy (24). In clinical practice, oncologists need to select a regimen considered to be the most appropriate for each individual patient based on the medical condition of each patient, including such factors as age, performance status, organ function and extent of disease. The cisplatin-based regimens are usually inappropriate to be used for patients having peritoneal dissemination and retention of ascites, because such patients have potential renal impairment or poor performance

Table 3. Responses to treatment (total of 355 administrations of the sequential MTX/5FU therapy)

	No. of evaluable patients	CR	PR	NC	PD	NE	Response rate (%)	95% CI (%)
Objective response	35	–	2	21	6	6	5.7	0.7–19.2
Response in ascites	37	3	10	15	6	3	35.1	20.2–52.5

CR, complete response; PR, partial response; NC, no change; PD, progressive disease; NE, not evaluable; CI, confidence interval.

status, which makes it difficult to tolerate the large volume hydration for the prevention of cisplatin-induced renal injury. Among several 5FU-based regimens, sequential MTX/5FU therapy is widely used because this regimen has definite anti-tumor activity against advanced gastric cancer with acceptable toxicity even in high-risk patients. The purpose of the present phase II study was to evaluate the efficacy and toxicity of the sequential MTX/5FU regimen in patients with unresectable gastric cancer with peritoneal dissemination accompanied by malignant ascites and to assess whether further investigation in a phase III setting is warranted.

Progression to peritoneal dissemination is very common in advanced gastric cancer and is frequently a component of the first episode of failure after surgery for primary gastric cancer (25). Therefore, intraperitoneal chemotherapy has previously been investigated for peritoneal dissemination for the purposes of palliation and the prevention of peritoneal metastasis after surgery in high-risk patients. The pharmacokinetic rationale for intraperitoneal therapy is that drug concentrations within the peritoneal cavity are several-fold to 1–2 logs higher than concentrations that can be achieved after oral or intravenous treatment (26,27). In ovarian cancer, a large randomized trial demonstrated a small but statistically and clinically significant survival advantage in patients receiving intraperitoneal therapy (28). However, generally the efficacy of intraperitoneal chemotherapy is considered to be modest because the penetration of intraperitoneally injected drug into submesothelial tissue is too limited to achieve anti-tumor activity. Moreover, intraperitoneal chemotherapy sometimes induces systemic adverse events similar to systemic chemotherapy in addition to local complications such as chemical peritonitis. No definite data are currently available to specify which treatment option, intraperitoneal or systemic chemotherapy, is more suitable for patients with peritoneal dissemination in terms of benefit regarding survival and quality of life.

When we perform systemic chemotherapy in patients who have fluid retention such as ascites or pleural effusion, we have to consider the pharmacokinetic alterations of the anti-tumor agents administered. Intravenously administered MTX penetrates the ascites or pleural effusion and the clearance rate of MTX from ascites and plasma is ~5 and ~120 ml/min, respectively (29). Therefore, the retention of body fluid prolongs the terminal plasma half-life of intravenously administered drug owing to the slow re-entry of the sequestered drug into the bloodstream. Such phenomena should be associated with both favorable anti-tumor activity against peritoneal or pleural dissemination and with the potential risk of systemic toxicity. In another phase II study of sequential MTX/5FU therapy against unresectable or metastatic gastric cancer previously conducted by the JCOG, in which the same dosage and schedule as in the present study were utilized but the patients having ascites were ineligible for entry (JCOG 9207 study), none of 56 enrolled patients experienced grade 3 or 4 neutropenia (data not shown). In the present study, grades 3 and 4 neutropenia were observed in six (16 %) and two patients (11 %), respectively. The incidence of leukopenia, anemia, increase in total bilirubin and increase in serum creatinine of grade 3 or 4 tended to be more frequent in the present study than in the JCOG 9207 study (data not shown). Therefore, the toxicity of the sequential MTX/5FU therapy might be more severe in patients with malignant ascites than in those without. Two treatment-related deaths were observed in the present study. These two patients developed progressive neutropenic sepsis, which is a major cause of death. Although these two patients had met the eligibility criteria required in the study, both patients were retrospectively shown to be at high-risk for neutropenic infection, because pretreatment serum CRP values were highly elevated in both patients and leukocytosis was also observed at the baseline in one patient. Therefore, we consider that patients with apparent inflammatory signs such as elevation of CRP or leukocytosis should be excluded from future studies to prevent neutropenic sepsis. It is known that the different methods of administration of 5FU, either as a bolus or by infusion, represent different efficacy and toxicity profiles, thus infusional 5FU has more clinical benefit in efficacy (response rate) and safety in metastatic colorectal cancer. At present, however, we do not have sufficient data to establish whether these clinical observations hold true in patients with peritoneal dissemination with malignant ascites and it seems to be important to investigate the infusional 5FU-based regimens in this clinical setting, which may contribute to reducing the toxicity.

It is difficult to evaluate the efficacy of chemotherapy against peritoneal dissemination in clinical trials as well as in clinical practice, because most disseminated tumor cells do not form a measurable mass but rather constitute a diffuse lesion. Clinicians have to assess the efficacy of treatment and disease status in each patient based on the integration of clinical information such as clinical imaging, tumor markers and clinical symptoms. In the present study, the therapeutic efficacy was assessed according to the specific criteria for the study based on the change in the volume of ascites visualized by abdominal CT scan or ultrasonography as a surrogate marker. Using these criteria, we found that the ascites disappeared or was decreased by the MTX/5FU therapy in 35% of the patients. Konishi et al.

also reported that ascites disappeared in 50% (8/16) of patients with peritoneal-disseminated gastric cancer after MTX/5FU therapy (16). These results show that sequential MTX/5FU therapy is effective in controlling malignant ascites and also suggest that this regimen is effective against peritoneal dissemination from advanced gastric cancer.

Although the present study was originally planned as a phase II study involving 50 patients, patient enrollment had been delayed and finally terminated before the projected number of patients was achieved. The delay in patient enrollment was probably caused by the eligibility criteria for this study. Although peritoneal dissemination of advanced gastric cancer is very common in clinical practice, most patients with peritoneal dissemination accompanied by malignant ascites tend to have relatively poor performance status and impaired organ function, which was considered to be a critical issue delaying patient enrollment. The JCOG monitoring committee accepted the investigators' decision that the objectives of this study, which were to calculate the response rate in ascites and to evaluate the safety of sequential MTX/5FU therapy for decision-making to pursue further investigation in a phase III study, were achieved even with the actual sample size of 37 patients and that the response rate in ascites of 35% (95% confidence interval: 20.2–52.5%) observed in this study was positive.

It is well known that peritoneal dissemination of gastric adenocarcinoma occurs more commonly as the histologically diffuse type than the intestinal type. Konishi et al. reported that sequential MTX/5FU therapy was more effective against undifferentiated gastric cancer (i.e. histologically diffuse type) than differentiated gastric cancer (i.e. histologically intestinal type), with a response rate of 32% (9 PRs/28 patients) vs 0% (0 PRs/10 patients) (16). A similar tendency was observed in the present study, namely that the response rate of ascites was higher for the histologically diffuse type than for the intestinal type (44%, 11 responders among 25 patients, versus 17%, two responders among 12 patients). The difference in the efficacy of the sequential MTX/5FU therapy depending on the histological type might be explained by the difference in the activities of two enzymes, thymidylate synthetase and thymidine kinase, in the various histological types of gastric cancer (30). However, other reports have suggested that there were no significant differences according to the histological type. (15)

In conclusion, the findings of the present study suggest that sequential MTX/5FU therapy is effective in controlling malignant ascites from gastric cancer with overall acceptable toxicity and that further investigations are warranted. However, the present study also suggests that severe toxicity may occur more frequently in patients with malignant ascites than in those without malignant ascites. Whether there is true clinical benefit in this regimen for patients with peritoneal dissemination from advanced gastric cancer should be evaluated in future randomized clinical trials. Since the peritoneal dissemination from gastric cancer is considered to be an incurable disease, the patient's survival and quality of life will be important endpoints to be assessed in the future clinical trials. Recently, various new drugs with different mechanisms of action have been developed. However, since the patients whose main diseases are peritoneal dissemination are usually excluded from the phase II trials of new drugs or new combination regimens because of the lack of measurable lesions in those patients, the available data as to the efficacy against peritoneal dissemination are very limited unless we conduct trials specifically designed for this purpose as the present study. We think it is important to assess the roles of new drugs from the viewpoint of how we can maximize the potential value of each drug or regimen in disease-specific clinical situations. In this study we have focused on peritoneal dissemination with malignant ascites from advanced gastric cancer, which is very common and a major clinical problem. At present, any 5FU-based combination chemotherapies cannot prolong overall survival compared with 5FU alone. However, the present study brought us to the hypothesis that if we choose an appropriate regimen and administer it to the appropriate patient population (for example, to choose MTX/5FU therapy for the patients with peritoneal dissemination), survival may be prolonged compared with 5FU alone. We think that MTX/5FU therapy is the most reasonable regimen to be tested as a first-line chemotherapy in patients with peritoneal dissemination from advanced gastric cancer. From this clinical standpoint, a phase III randomized controlled trial comparing sequential MTX/5FU therapy with infusional 5FU-monotherapy (800 mg/m^2 of 5FU continuous infusion over 5 days every 4 weeks) in patients with advanced gastric cancer who have peritoneal dissemination with or without ascites is currently being carried out by the Japan Clinical Oncology Group (JCOG 0106-MF study). As a final note, we suggest that in future trials we should investigate the therapeutic strategy not only with newer cytotoxic drugs including irinotecan, taxanes and oxaliplatine, but also with new molecular targeting drugs such as antibody, VEGF drugs and EGF drugs, to bring about a breakthrough in this dire clinical condition.

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Original article

Identification of risk factors for the development of complications following extended and superextended lymphadenectomies for gastric cancer

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Background: Extended lymphadenectomy for gastric carcinoma has been associated with high mortality and morbidity rates in several multicentre randomized trials.

Methods: Using data from 523 patients registered for a prospective randomized trial comparing extended (D2) and superextended (D3) lymphadenectomies, risk factors for overall complications and major surgical complications (anastomotic leakage, intra-abdominal abscess and pancreatic fistula) were identified by multivariate logistic regression analysis.

Results: Mortality and morbidity rates were 0·8 per cent (four of 523) and 24·5 per cent (128 of 523) respectively. Pancreatectomy (relative risk 5·62 (95 per cent confidence interval (c.i.) 1·94 to 16·27)) and prolonged operating time (relative risk 2·65 (95 per cent confidence interval 1·34 to 5·23)) were the most important risk factors for overall complications. A body mass index of 25 kg/m^2 or above, pancreatectomy and age greater than 65 years were significant predictors of major surgical complications.

Conclusion: Pancreatectomy should be reserved for patients with stage T4 disease. Age and obesity should be considered when planning surgery.

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Introduction

Despite a declining incidence in Western Europe[1] and the USA[2], gastric carcinoma remains the second commonest cause of cancer death worldwide, with over 600 000 deaths per year[3]. Given the poor outcome of irresectable disease treated by other therapeutic modalities in phase II and III trials[4,5], the curative treatment of gastric carcinoma remains primarily surgical. Although the presence of distant metastases usually precludes curative surgery, this does not necessarily apply to disease in the regional lymph nodes, which can be dissected *en bloc* with the primary lesion[6,7]. This type of resection may allow cure, provided that metastases are within the margins of dissection. Removal of a wider range of lymph nodes by extended lymph node dissection might increase the chance of cure, but is inappropriate if the cancer has spread systemically.

In Japan, gastrectomy plus extended systematic lymphadenectomy (D2 resection) has long been the standard treatment, even for superficial cancers[8]. Success with D2 resection has led to the evolution of a superextended lymphadenectomy (D3 resection) and several feasibility studies evaluating dissection of para-aortic lymph nodes have been performed[9–12]. A randomized trial (Japan Clinical Oncology Group (JCOG) 9501) was launched in 1995, primarily to explore the potential survival benefit of D3 over D2 dissection[13]. This trial has provided the opportunity to evaluate prospectively collected data on gastric cancer surgery in Japan. The present study represents a detailed analysis of risk factors for overall and surgical complications following D2 and D3 resections.

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Patients and methods

Between June 1995 and April 2001, 523 patients registered in the JCOG 9501 study were allocated randomly to either D2 (263 patients) or D3 (D2 plus para-aortic lymph node dissection; 260 patients) resection. Eligibility criteria and the method of randomization have already been reported in detail[13]. In brief, patients aged less than 75 years of age with histologically proven and resectable primary gastric carcinoma with an estimated depth of SS (penetrating the muscle layer), SE (penetrating the serosa) or SI (invasion to an adjacent organ) were recruited after giving informed consent. Patients found positive for free cancer cells by cytological examination of peritoneal washes and those with Borrmann type 4 tumours (linitis plastica type) were excluded. Twelve institutions participated in the trial initially and 12 other institutions were added to increase patient recruitment.

After laparotomy, cytological examination of peritoneal washes was performed, followed by gross examination of the abdominal cavity and the primary lesion. Only patients who were negative for free cancer cells in the abdominal cavity and without evidence of gross para-aortic lymph node spread, peritoneal carcinomatosis or other distant metastasis were eligible to participate. The patients were allocated randomly to either D2 or D3 resection by the minimization method of balancing the groups according to T stage (T2 *versus* T3/T4), gross appearance (Borrmann types 1 and 2 *versus* Borrmann types 3 and 5) and institution. The surgeons were notified immediately of the allocation results and completed the operation accordingly.

Patients underwent appropriate gastrectomy with systematic lymphadenectomy as allocated. Perigastric lymph nodes (nodal stations 1, 3, 4, 5 and 6 according to the Japanese Classification of Gastric Cancer[14]) and nodes at the base of the left gastric artery (7), along the common hepatic artery (8) and at the base of the splenic artery (11) were resected routinely. Lymph nodes along the hepatoduodenal ligament and behind the pancreatic head (12 and 13) were resected when the primary lesion was located in the lower third of the stomach. Lymph nodes along the left side of the cardia (2), within the splenogastric ligament (4sa) and at the splenic hilum (10) were resected with the spleen when total or proximal gastrectomy was performed. Concurrent resection of the pancreatic tail was not routine during either D2 or D3 resection and was reserved for patients with direct invasion to the pancreas. In patients randomized to superextended lymphadenectomy, para-aortic lymph nodes from the level of the coeliac trunk down to the root of the inferior mesenteric artery (16a2 and 16b1) were dissected. The mode of reconstruction following resection was not specified.

All information on complications was extracted from the case-report forms for the trial. Anastomotic leakage, intra-abdominal abscess and pancreatic fistula were considered to be major surgical complications. Anastomotic leakage was defined as dehiscence confirmed by radiographic examination using contrast medium. Pancreatic fistula was diagnosed if there was prolonged purulent discharge containing pancreatic juice from the drainage tube.

Factors that might affect the risk of overall and major surgical complications were evaluated by univariate analysis using cross-tabulations. Variables analysed included extent of lymphadenectomy, splenectomy, pancreatectomy, type of gastrectomy, pathological (p) T category (pT2 and pT3 *versus* pT4), sex, age, body mass index (BMI), operating time, amount of blood loss and need for autologous blood transfusion. Operating time and blood loss were divided into tertiles for analysis. Two factors associated with surgical experience were also evaluated: institutions that enrolled over 20 patients *versus* those with fewer patients and first and second halves of the trial (1995–1998 *versus* 1999–2001). The χ^2 test was used to assess differences in proportions. The independent contribution of various factors was assessed by multivariate logistic regression analysis, with mutual adjustment of potential risk factors for complications. All factors analysed in the univariate analysis were included as variables in the multivariate analysis. Two-sided P values are presented. Statistical analysis was performed using SAS® version 8.12 (SAS Institute, Tokyo, Japan).

Results

Total gastrectomy was performed in 199 (38·0 per cent) of 523 patients and proximal gastrectomy in four;

Table 1 Complications

Severe abdominal complications	
Pancreatic fistula	30
Abdominal abscess	29
Anastomotic leakage	11
Other complications	
Pneumonia	16
Anastomotic stenosis	14
Bowel obstruction/ileus	16
Lymphorrhoea	10
Thoracic effusion requiring thoracic drainage	7
Severe feeding problem requiring prolonged hyperalimentation	6
Wound abscess	5
Postoperative bleeding	3
Severe diarrhoea	3
Urinary tract infection	3
Catheter-induced sepsis	3
Pulmonary embolism	2
Cardiac failure	1
Cholecystitis requiring percutaneous drainage	1

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the remaining patients underwent distal gastrectomy. Splenectomy was performed in 191 patients (36·5 per cent) and distal pancreatectomy in 22 (4·2 per cent). There was no significant difference in the type of gastrectomy and incidence of combined resection between the two groups. Details of patient demographics and tumour stages have been reported previously[13].

There were four hospital deaths (0·8 per cent), two in each group. Two patients suffered from rapid disease progression and died 3 and 5 months after surgery without being discharged from hospital. One patient died from pneumonia at 46 days and another died from massive bleeding from the gastroduodenal artery 24 days after operation. Complications were identified in 128 patients (24·5 per cent) and major surgical complications in 49 patients (9·4 per cent) (*Table 1*).

The results of univariate analyses of risk factors for overall postoperative complications are summarized in *Table 2*. Only pancreatic resection ($P = 0·001$) and

Table 2 Univariate and multivariate analysis of risk factors for overall complications

			Univariate analysis		Multivariate analysis	
	n	No. with complications	Relative risk	*P*	Relative risk	*P*
Extent of lymphadenectomy						
D2	263	55	1		1	
D3	260	73	1·48 (0·99, 2·21)	0·057	0·93 (0·58, 1·51)	0·776
Splenectomy						
No	332	64	1		1	
Yes	191	64	2·11 (1·41, 3·17)	< 0·001	2·05 (0·52, 8·01)	0·304
Pancreatectomy						
No	501	115	1		1	
Yes	22	13	4·85 (2·02, 11·63)	< 0·001	5·62 (1·94, 16·27)	0·001
Extent of gastrectomy						
Distal	320	62	1		1	
Total or proximal	203	66	2·01 (1·34, 3·00)	< 0·001	0·84 (0·22, 3·27)	0·804
Invasion to adjacent organs						
T2, T3	501	123	1		1	
T4	22	5	0·90 (0·33, 2·50)	0·846	0·37 (0·11, 1·24)	0·107
Sex						
M	358	94	1		1	
F	165	34	0·73 (0·47, 1·14)	0·163	0·73 (0·45, 1·19)	0·207
Age (years)						
< 56	160	33	1		1	
56–65	207	48	1·16 (0·70, 1·92)	0·557	1·26 (0·73, 2·17)	0·403
> 65	156	47	1·66 (0·99, 2·77)	0·053	1·63 (0·92, 2·89)	0·092
Body mass index						
< 25	446	101	1		1	
≥ 25	77	27	1·85 (1·10, 3·10)	0·019	1·75 (0·99, 3·08)	0·054
Operating time (min)						
< 240	167	23	1		1	
240–297	179	43	1·98 (1·13, 3·46)	0·016	1·77 (0·96, 3·25)	0·068
> 297	177	62	3·38 (1·97, 5·78)	< 0·001	2·65 (1·34, 5·23)	0·005
Blood loss (ml)						
< 395	174	27	1		1	
395–710	174	42	1·73 (1·01, 2·97)	0·045	1·05 (0·58, 1·90)	0·886
> 710	175	59	2·77 (1·65, 4·64)	< 0·001	1·11 (0·58, 2·12)	0·754
Blood transfusion						
Yes	408	87	1		1	
No	115	41	2·04 (1·31, 3·20)	0·002	1·53 (0·92, 2·56)	0·102
Case volume*						
< 20	147	41	1		1	
≥ 20	376	87	0·78 (0·51, 1·20)	0·256	0·83 (0·51, 1·34)	0·437
Period						
1995–1998	295	75	1		1	
1999–2001	228	53	0·9 (0·59, 1·33)	0·566	0·87 (0·56, 1·35)	0·539

Values in parentheses are 95 per cent confidence intervals. *No. of patients registered.

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Table 3 Univariate and multivariate analysis of risk factors for major surgical complications

			Univariate analysis		Multivariate analysis	
	n	No. with major complications	Relative risk	*P*	Relative risk	*P*
Extent of lymphadenectomy						
D2	263	23	1		1	
D3	260	26	1·16 (0·64, 2·09)	0·623	0·67 (0·32, 1·39)	0·279
Splenectomy						
No	332	20	1		1	
Yes	191	29	2·79 (1·53, 5·09)	< 0·001	1·08 (0·15, 7·56)	0·941
Pancreatectomy						
No	501	43	1		1	
Yes	22	6	3·99 (1·49, 10·74)	0·003	6·90 (1·86, 25·58)	0·004
Extent of gastrectomy						
Distal	320	19	1		1	
Total or proximal	203	30	2·74 (1·50, 5·03)	< 0·001	2·15 (0·31, 15·20)	0·442
Invasion to adjacent organs						
T2, T3	501	47	1		1	
T4	22	2	0·97 (0·22, 4·26)	0·964	0·37 (0·067, 2·01)	0·246
Sex						
M	358	38	1		1	
F	165	11	0·60 (0·30, 1·21)	0·150	0·57 (0·25, 1·27)	0·169
Age (years)						
< 56	160	7	1		1	
56–65	207	20	2·34 (0·96, 5·67)	0·061	3·06 (1·15, 8·20)	0·026
> 65	156	22	3·59 (1·49, 8·66)	0·005	4·04 (1·48, 11·02)	0·006
Body mass index						
< 25	446	34	1		1	
≥ 25	77	15	2·93 (1·51, 5·69)	0·001	3·32 (1·54, 7·12)	0·002
Operating time (min)						
< 240	167	8	1		1	
240–297	179	14	1·69 (0·69, 4·13)	0·252	1·60 (0·60, 4·27)	0·350
> 297	177	27	3·58 (1·58, 8·12)	0·002	2·96 (1·03, 8·55)	0·045
Blood loss (ml)						
< 395	174	10	1		1	
395–710	174	11	1·11 (0·46, 2·68)	0·822	0·47 (0·17, 1·30)	0·145
> 710	175	28	3·12 (1·47, 6·65)	0·003	0·86 (0·32, 2·31)	0·767
Blood transfusion						
Yes	408	29	1		1	
No	115	20	2·75 (1·49, 5·08)	< 0·001	1·99 (0·97, 4·08)	0·061
Case volume*						
< 20	147	16	1		1	
≥ 20	376	33	0·79 (0·42, 1·48)	0·457	0·76 (0·36, 1·57)	0·454
Period						
1995–1998	295	30	1		1	
1999–2001	228	19	0·80 (0·44, 1·47)	0·475	0·83 (0·43, 1·61)	0·575

Values in parentheses are 95 per cent confidence intervals. *No. of patients registered.

prolonged operating time (patients in the upper tertile for whom the operating time was more than 297 min; $P = 0·005$) were identified as significant independent risk factors for overall complications (*Table 2*). A BMI of 25 or more was close to significance ($P = 0·054$).

The results of univariate analyses of risk factors for major surgical complications are summarized in *Table 3*. Multivariate analysis identified BMI ($P = 0·002$), pancreatic resection ($P = 0·004$), age (56–65 years, $P = 0·026$; over 65 years, $P = 0·006$) and operating time over 297 min ($P = 0·045$) as significant independent risk factors for major surgical complications (*Table 3*).

Discussion

Gastrectomy plus extended systemic lymphadenectomy (D2 resection) is the standard procedure for gastric carcinoma in Japan. This approach has resulted in superior stage-by-stage survival than that observed in most Western countries and has led to cure for a

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proportion of patients with nodal disease beyond the perigastric region, although this has not been confirmed in Western randomized trials[15,16]. Although long-term follow-up revealed significantly better disease-free survival for the D2 group in the subset with node-positive cancer[17], this difference did not extend to all patients in the trial, in part owing to the unacceptably high mortality rate associated with D2 resection[8]. JCOG 9501, a Japanese multi-institutional prospective randomized trial comparing D2 with more extended resection, has superior quality control of surgical procedures and reliability of data[13] than retrospective Japanese studies and Western prospective trials.

The most significant risk factor for both surgical and overall complications in the present study was pancreatic resection, although it should be noted that this was performed in only 4·2 per cent of patients, compared with 30·3 and 15·2 per cent in the UK Medical Research Council (MRC) and Dutch trials respectively[15,16]. The rate of pancreatectomy was lower in the present series because a pancreas-preserving technique[18,19] was generally used, whereas distal pancreatectomy and splenectomy were integral parts of D2 dissection in the Dutch trial unless cancer was located in the distal stomach. The low morbidity rate in the present study may well be related to pancreas preservation[18,19]. The success of this approach has also been reported in a multicentre phase II trial of D2 dissection in Northern Italy[20].

Splenectomy, on the other hand, was not an independent determinant of risk, possibly because it was never performed with distal gastrectomy in the present series. In the Dutch randomized trial a high mortality rate after distal gastrectomy was attributed in part to necrosis of the remnant stomach as a result of splenectomy and division of the short gastric arteries[21]. The survival benefit of splenectomy performed solely to facilitate dissection of lymph nodes close to the splenic hilum has been questioned, however, and a randomized trial to explore this issue is ongoing[22].

Age was not an independent risk factor for overall complications in this study, in contrast to the Dutch trial in which age over 65 years was a significant risk factor for hospital death and overall complications[21]. This discrepancy may be attributed to the fact that only patients aged 75 years or less were eligible for inclusion in the JCOG 9501[13], whereas other trials have included older patients[15,16]. Japanese patients were, on average, 8 years younger than Dutch patients[23]; consequently the proportion of patients over 65 years of age was 29·8 per cent in the present series as opposed to 51·3 per cent in the Dutch trial[16]. This age distribution may account for the very low incidence of perioperative cardiovascular events in the present series, another factor that may have influenced the low morbidity and mortality rates.

Extended lymph node dissection may be hampered by excess bodyweight[24–26] and in the present study BMI was a significant risk factor for major surgical complications. Caucasians in general have a higher BMI than Japanese and the incidence of morbid obesity is significant among patients in the USA and Europe. Only 14·7 per cent of the present patients had a BMI of 25 kg/m^2 or greater, whereas one-third of the US population is obese (BMI over 27 kg/m^2)[27]. These data suggest that the patients' physique favours Japanese patients when major gastric cancer surgery is performed.

The extent of lymph node dissection (D2 *versus* D3), surgical volume and the period in which the operation was performed had no impact, suggesting that there were no learning curve issues. Although D2 resection has long been a standard procedure in Japan, all surgeons in the trial were experts from specialized centres who had sufficient experience with D3 resection through numerous other studies. Of the variables reflecting difficulties encountered during surgery, prolonged operating time was identified as a significant independent risk factor for both overall and major surgical complications. However, amount of blood loss and blood transfusion were significant only in univariate analysis; this may be attributable to multicolinearity, as these two factors are closely related.

Gastrectomy with extended lymphadenectomy is feasible and safe in Japan, provided that older patients with co-morbidity are excluded and pancreatectomy is reserved for lesions with direct invasion to the pancreas. Obese patients should be treated with caution, however, as they have a significant risk of developing major surgical complications. Hopefully, with careful patient selection, appropriate surgical expertise and pancreas and spleen preservation[8] where possible, equally good results, rarely achieved previously[20,28], will be realized in the West.

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ORIGINAL REPORT

Gastric Cancer Surgery: Morbidity and Mortality Results From a Prospective Randomized Controlled Trial Comparing D2 and Extended Para-Aortic Lymphadenectomy—Japan Clinical Oncology Group Study 9501

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Authors' disclosures of potential conflicts of interest are found at the end of this article

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A B S T R A C T

Purpose
Radical gastrectomy with regional lymphadenectomy is the only curative treatment option for gastric cancer. The extent of lymphadenectomy, however, is controversial. The two European randomized trials only reported an increase in operative morbidity and mortality, but failed to show survival benefit, in the D2 lymphadenectomy group. We conducted a randomized controlled trial to compare the Japanese standard D2 and D2 + para-aortic nodal dissection.

Patients and Methods
Only experienced surgeons in both procedures from 24 Japanese institutions participated in the study. Patients with potentially curable gastric adenocarcinoma (T2-subserosa, T3, or T4) who were surgically fit were intraoperatively randomized. Postoperative morbidity and hospital mortality were recorded prospectively in a fixed format and were compared between the two groups in this study.

Results
A total of 523 patients were randomized between July 1995 and April 2001. Postoperative complications were reported in 24.5% of all patients. Although the morbidity for the extended surgery group (28.1%) was slightly higher than the standard group (20.9%), there was no difference in the incidence of four major complications (anastomotic leak, pancreatic fistula, abdominal abscess, pneumonia) between the two groups. Hospital mortality was reported at 0.80%: one patient in each group died of operative complications, while one from each group died of rapid progressive cancer while inpatient.

Conclusion
Specialized surgeons could safely perform gastrectomy with D2 lymphadenectomy in patients with low operative risks. Para-aortic lymphadenectomy could be added without increasing major surgical complications in this setting.

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Gastric cancer is the second most common malignancy in the world, and surgical resection remains the only curative treatment option. Lymph node metastases occur during the early stages of this disease, and regional lymphadenectomy is recommended as part of radical gastrectomy. However, the extent of lymphadenectomy to achieve the optimal result is controversial, and there is no worldwide consensus.

Japanese surgeons first introduced the extended lymphadenectomy procedure, known today as D2, in the 1960s.[1] This technique requires the systematic dissection of lymph nodes in the first tier (perigastric) and the second tier (along the celiac artery and its branches). Early studies have reported that between 30% to 40% of patients

Table 1. Eligibility Criteria of the Study

Before operation
Entry criteria
Histologically proven adenocarcinoma
75 years or younger
Forced expiratory volume in 1 second ≥ 50%
Arterial oxygen pressure in room air ≥ 70 mm Hg
Creatinine clearance ≥ 50 mL/min
Written consent
Exclusion criteria
Carcinoma in the remnant stomach
Borrmann type 4 (linitis plastica)
Synchronous or metachronous malignancy in other organs except for cervical carcinoma in situ and colorectal focal cancer in adenoma
Past history of myocardial infarction or positive results of exercise ECG
Liver cirrhosis or chronic liver disease with indocyanine green test ≥ 10%
During operation
Macroscopic T staging is T2-subserosa, T3, or T4
Potentially curative operation is possible
No gross metastasis in para-aortic nodes (frozen section diagnosis not allowed)
Peritoneal lavage cytology is negative for cancer cells

with positive lymph node metastases including the second tier lymph nodes, have survived longer than 5 years with D2 lymphadenectomy.[2] However, D2 gastrectomy has a steep learning curve,[3] and may be associated with a higher-than-expected operative morbidity and mortality.

Two European randomized controlled trials comparing D1 and D2 gastrectomy revealed a high operative mortality exceeding 10% in the D2 group.[4,5] Based on these reports, the British National Health Service Cancer Guidance discourages the use of D2 technique in routine clinical practice.[6] In contrast, D2 gastrectomy is considered a standard and safe procedure in Japan, where 100,000 cases of gastric cancers are diagnosed every year. General surgeons are taught this technique early during their surgical training.[7] The Japanese nationwide registry reported an operative mortality of less than 2%, and in specialized institutions, less than 1% for D2 gastrectomy.[8,9]

Since the eighties, even more radical extended lymphadenectomy procedures had been practiced in many Japanese specialized centers. It was reported that 20% to 30% of patients with nonearly gastric cancer had microscopic metastasis present in the para-aortic nodes.[10-13] The 5-year survival for these patients has reached 14% to 30% after extended systematic dissection. In addition to D2 lymphadenectomy, lymph nodes around the upper abdominal aorta were dissected, primarily for ultimate local tumor control. However, this extended dissection may not only increase operative morbidity but also may effect the function of other abdominal organs.

There has never been a prospective study to assess the perioperative morbidity and mortality in Japanese patients after D2 gastrectomy or more extended surgery. To evaluate the survival benefit and operative complications of D2 gastrectomy and extended para-aortic dissection in gastric cancer surgery, a multi-institutional randomized controlled trial was conducted on behalf of the Japan Clinical Oncology Group (JCOG). The accrual closed with 523 patients. We hereby present the data on the operative morbidity and mortality, which are the secondary end points of this trial. Survival analysis is scheduled to take place in August 2006.

Objectives and End Points of the Study

A prospective randomized controlled trial was designed to compare the two surgical techniques: the standard lymphadenectomy and the standard lymphadenectomy with the addition of para-aortic node dissection for gastric cancer. Only surgeons with sufficient experience of para-aortic dissection for gastric cancer participated in the trial. Since the role of neoadjuvant and adjuvant chemotherapy was not established, no patients received chemotherapy until recurrent disease was diagnosed.

The primary end point was the overall survival, while the secondary end points were the relapse-free survival, operative morbidity, hospital mortality, and quality of life. Randomization and data handling for this study was performed by the Data Centre of the JCOG, a government-sponsored organization for multi-institutional clinical trials.[14]

Eligibility Criteria

Eligibility criteria for this study are shown in Table 1. Patients with advanced gastric cancer deemed curable and fit for surgery were recruited into the trial following informed consent. Borrmann type 4 tumors (linitis plastica) were excluded because of their very poor prognosis after surgery. Liver cirrhosis and ischemic heart disease were important risk factors for mortality after surgery and hence were excluded from the study. Para-aortic lymph node metastasis is extremely rare in T1 (invasion confined

to the mucosa or submucosa) and T2-MP tumors (invasion confined to the muscularis propria); hence, these patients were not eligible for randomization. Only patients diagnosed with T2-SS (subserosal invasion) or deeper tumors at the time of laparotomy were included in the study. T2-SS is clinically recognized as a white discoloration on the serosal surface, without overt tumor serosal exposure.

During the operation, the para-aortic nodes were inspected to exclude patients with gross metastasis (enlarged and/or hard nodes) in this region. Frozen section diagnosis of the para-aortic nodes was forbidden to avoid technical contamination between the two groups of patients. Peritoneal lavage cytology was performed immediately after initial laparotomy, and absence of free cancer cells was confirmed before enrollment.

Random Assignment

While waiting for the result of lavage cytology, the surgeon examined the above eligibility criteria and started the D2 procedure. When the negative cytology result was obtained 30 to 60 minutes later, he informed the JCOG Data Centre for enrollment. Patients were then randomly assigned either to receive standard lymphadenectomy (group A) or extended lymphadenectomy (group B). The sizes of the groups were balanced according to T stage (T2 *v* T3/T4), tumor growth pattern (expansive *v* infiltrative growth), and institution. The randomization arm was notified to the surgeon immediately, who then completed the operation according to the allocated protocol.

Surgical Methods

Group A: Standard D2 gastrectomy. Patients were treated with gastrectomy and D2 lymphadenectomy. Depending on the location of the primary tumor, the surgeon performed either a total, proximal subtotal, or distal subtotal gastrectomy. D2 lymphadenectomy was a standard procedure for dissection of tumors located in the upper two thirds of the stomach as defined in the 12th edition of the Japanese Classification (1993)[15] when the study was initially designed. An extended D2 lymphadenectomy was performed for tumors located in the lower third of the stomach, which involves further dissecting the hepatoduodenal nodes (No.12a), retropancreatic nodes (No.13) and nodes along the superior mesenteric vein (No.14v). This technique was frequently performed as a standard procedure in the specialized centers, and thus adopted in this study (all except No.13 have been integrated as "D2" in the 13th edition of Japanese classification[16]).

In total or proximal subtotal gastrectomy for proximal tumors, the spleen was removed in principle for splenic hilar lymphadenectomy, while it was preserved in distal subtotal gastrectomy for distal tumors.

Group B: D2 gastrectomy combined with para-aortic lymphadenectomy. Patients in this group had similar procedure to group A, but with additional para-aortic lymph node dissection. The area to be dissected was defined in the Japanese classification (Fig 1). Proximal tumors were treated with the standard D2 lymphadenectomy, and also all "No.16-a2" (para-aortic nodes between the level of the celiac axis and the left renal vein) and "No.16-b1" (para-aortic nodes between the left renal vein and the inferior mesenteric artery) were removed. Standard distal subtotal gastrectomy was performed for the distal tumors including the "No.16-a2" and "No.16-b1" nodes; however, dissection of the left upper lateral nodes ("No.16-a2-lat") was optional.

Both group A and group B patients were followed up according to a fixed schedule, without receiving adjuvant chemotherapy.

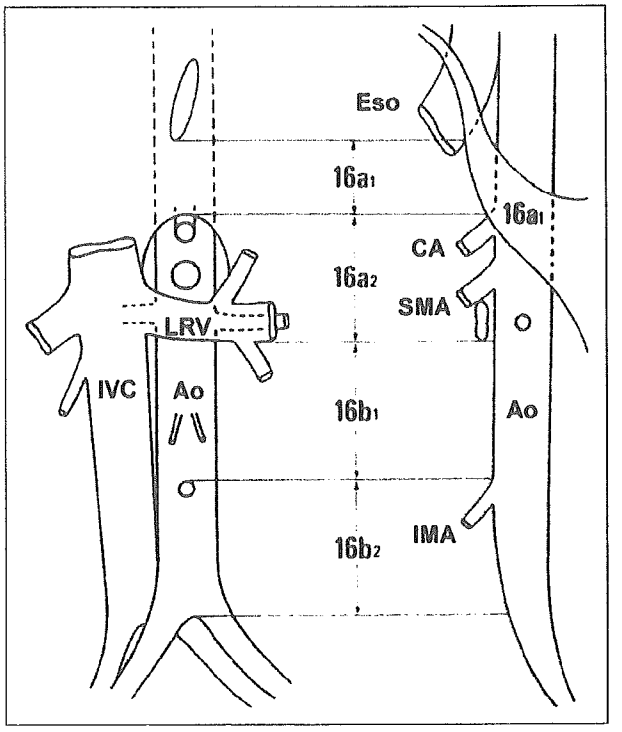

Fig 1. Anatomic definitions of para-aortic lymph nodes.[15] The nodes No.16a2 and No.16b1 are defined as "regional nodes" and were dissected in the extended surgery group. Ao, aorta; CA, celiac artery; Eso, esophagus; IMA, inferior mesenteric artery; IVC, inferior vena cava; LRV, left renal vein; SMA, superior mesenteric artery.

Evaluation of Operative Morbidity and Mortality

Operative methods and pathology results were recorded according to the 12th edition of the Japanese Classification of Gastric Carcinoma.[15] The following information was included on the case report form for prospective data collection concerning the four major groups of operative morbidity: presence or absence of anastomotic leak, pancreatic fistula, abdominal abscess, and pneumonia. Anastomotic leak was diagnosed radiologically either on routine postoperative contrast swallow or based on clinical suspicion, and was recorded regardless of its clinical significance. Pancreatic fistula was usually diagnosed when fluid with a high amylase concentration drained from the peripancreatic area for more than 7 days.

Other complications were recorded on a free format. The duration of surgery, blood loss, blood transfusion requirement and reoperation details were also recorded. Hospital mortality was defined as postoperative death of any cause within 30 days, or death within the same hospitalization.

Sample Size

The projected 5-year survival rates for groups A and B patients were 50% and 62%, respectively, and we initially planned to recruit 412 patients (206 each group) to detect this difference with one-sided α error of .05 and statistical power of 80%. At first, the recruitment was slow, but it improved as the study progressed. When the planned recruitment was almost achieved, the JCOG Clinical Trial Review Committee approved the amendment to increase the number of patients to 520 (260 each group) to

Table 2. Patients' Demographics and Tumor Characteristics

	Group A (n = 263)	Group B (n = 260)	Total (N = 523)
Male-female ratio	176/87 = 2.02	182/78 = 2.33	358/165 = 2.17
Age, years			
Median	60	61	61
Range	25-75	27-75	25-75
Tumor diameter, cm			
Median	5.5	5.5	5.5
Range	2-17	2-15.2	2-17
T-stage (macroscopic)			
T2-SS	99	93	192
T3	150	159	309
T4	14	8	22
Tumor location			
Upper 1/3	53	47	100
Middle 1/3	103	103	206
Lower 1/3	107	110	217

NOTE. All data are numbers of patients except where otherwise indicated.
Abbreviation: SS, subserosal invasion.

enforce the statistical power to detect 8% difference in the 5-year survival rates, with a 5.5-year accrual period and an additional 5-year follow-up.

Institutions and Quality Control of Surgery

The approval of the institutional review board from all participating institutions was obtained. Initially, the 12 institutions of the Gastric Cancer Surgical Study Group of the JCOG participated in the trial. Twelve institutions were added to increase patient recruitment before February 1999.

All participating surgeons agreed to the technical details for surgery during the planning stages of this trial. Significant experience in gastric cancer surgery, especially experience in extended lymphadenectomy, was a prerequisite for a surgeon's participation in the trial. Surgeons with experience of more than 100 D2 gastrectomies, or institutions with a specialized unit with annual gastrectomy volume of 80 cases or more were selected.

During the recruitment period, participating surgeons and Data Centre representatives met three times per year to monitor the study. In each meeting, videos of para-aortic dissection were presented for critique from four or five institutions, and the technical details were discussed. To assess compliance with lymphadenectomy, dissection, node recovery status in all nodal "stations," and the number of dissected nodes in the para-aortic area were recorded in the case report form, and the results were monitored.

Statistical Methods

The operative morbidity and mortality rates were based on the proportion of the number of cases divided by all registered patients based on the intention-to-treat principle. The differences in proportion between groups were evaluated using Fisher's exact test. Differences in length of hospital stay and blood loss were compared by Wilcoxon test. All P values are two-sided, and statistical analysis was done using SAS (SAS Institute, Cary, NC) version 8.12.

Recruitment

Recruitment commenced in July 1995, and closed in April 2001. A total of 523 patients were enrolled: 263 in group A and 260 in group B. A large variance was observed for the number of patients recruited between the institutions. Fifty-three percent of all patients were recruited by the five major hospitals.

The JCOG site-visit audit reported that written consent was available for all except nine patients from one institution. In another institution, an additional six patients had informed consent submitted by a family member.

Patients and Surgery

Patient demographics and tumor characteristics are presented in Table 2. The two groups were well balanced, as there were no significant differences in their baseline data.

The operative details are shown in Table 3. Total gastrectomy was performed in 38% of all patients, and the vast majority of total gastrectomies (186 of 199 cases) were accompanied by splenectomy. Pancreatectomy was confined to those patients whose pancreas was involved by tumor, accounting for 11% of all total gastrectomies. In four cases, proximal subtotal gastrectomy with splenectomy was performed instead of total gastrectomy. Para-aortic lymphadenectomy required longer operation time (median, 63 minutes) and resulted in greater blood loss (median, 230 mL) than the standard D2. Blood transfusion was required approximately twice as often.

Protocol Violation and Ineligible Cases

There were 10 cases of protocol violation (1.9%). In one case, the para-aortic nodes were examined by frozen

Japanese multicenter phase II study of CHOP followed by radiotherapy in stage I–II_1, diffuse large B-cell lymphoma of the stomach

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CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) followed by radiotherapy is regarded as standard care for localized aggressive lymphoma; however, prospective confirmation of its applicability to localized primary gastric lymphoma is inadequate, and most patients in Japan have been initially treated with gastrectomy. We conducted a multicenter phase II study to evaluate the feasibility and efficacy of the non-surgical treatment. Eligibility criteria required primary gastric diffuse large B-cell lymphoma, stage I–II_1, age 20–75, performance status 0–1 and adequate organ function. Treatment consisted of three cycles of CHOP followed by radiotherapy 40.5 Gy. Fifty-five patients were enrolled between December 1999 and February 2003, and 52 eligible patients were analyzed. Patient characteristics were as follows: median age, 61 years; 28 men, 24 women; 36 with stage I, 16 with stage II_1; 47 with a low International Prognostic Index (IPI) and five with a low–intermediate IPI. All but one patient completed planned treatment. No serious complications including massive hemorrhage or perforation were observed. A complete response was achieved in 48 of the 52 patients (92%, 95% confidence interval: 82–98%) and progressive disease in three. Two patients underwent salvage gastrectomy due to disease persistence or recurrence. With a median follow-up period of 28 months, 2-year progression-free and overall survivals were 88 and 94%, respectively. CHOP followed by radiotherapy is safe and highly effective in localized gastric diffuse large B-cell lymphoma. This organ-preserving treatment should be considered as a very reasonable therapeutic option. (*Cancer Sci* 2005; 96: 349–352)

Primary gastric lymphoma (PGL) is the most common among extranodal non-Hodgkin's lymphomas. PGL includes various histologic subtypes and management decisions are made depending on these subtypes. Eradication of *Helicobacter pylori* can achieve a 60–90% complete response for localized gastric mucosa-associated lymphoid tissue (MALT) lymphoma,[1] and this stomach-preserving treatment has been rapidly accepted. In contrast, the optimal treatment of localized gastric diffuse large B-cell lymphoma (DLBCL) still remains controversial. Surgery, alone or followed by chemotherapy with or without radiotherapy (RT), has been used as a primary therapy[2–5] and has been supported by many physicians. Stomach-preserving treatment with chemotherapy with or without RT has also been reported with encouraging results, but no definitive conclusion could be drawn because most series were retrospective with small numbers of patients, heterogeneous histologic subtypes and various combinations of treatment.[6–10]

CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) has been used as a standard chemotherapy for DLBCL and three cycles of CHOP followed by RT has also been accepted for localized DLBCL.[11] However, prospective clinical trials to confirm its applicability to primary gastric DLBCL have rarely been conducted. To evaluate the feasibility and efficacy of non-surgical treatment, we conducted a multicenter phase II study.

Materials and methods

Eligibility criteria and pretreatment evaluation. Eligibility criteria were as follows: pathologically proven primary gastric DLBCL; stage I II_1 (Lugano staging system for gastrointestinal (GI) lymphomas[12]); age 20–75; performance status (based on Eastern Cooperative Oncology Group scale) 0–1; no prior therapy; and adequate organ function. All patients gave written informed consent in accordance with our institutional review boards.

Pretreatment evaluation included history and physical examination, complete blood count, serum chemistries, gastroscopy with biopsy, barium enema or colonoscopy, endoscopic ultrasound of the stomach, computed tomography (CT) scan of the chest and the abdomen, bone marrow aspiration, electrocardiogram and cardiac ultrasonography. Gallium scintigram and barium swallow were optional.

Treatment details. The treatment consisted of three cycles of CHOP (day 1: cyclophosphamide, 750 mg/m^2; day 1: doxorubicin, 50 mg/m^2, day 1: vincristine, 1.4 mg/m^2 (capped at 2 mg); and days 1–5: oral prednisone, 100 mg) every 3 weeks. RT delivered with megavoltage equipment began 3–4 weeks after the third cycle of CHOP, confirming the recovery from the toxicity of chemotherapy. The primary tumor and the metastatic lymph nodes were irradiated for a total dose of 40.5 Gy in 27 fractions over 5.5 weeks. Regional perigastric lymph nodes were also irradiated electively for a total dose of 30 Gy in 20 fractions. Conventional 2-D RT was allowed in the protocol of the present study, and dose constraints to risk organs were as follows: doses to the kidneys, no more than 50% of both kidneys should receive ≥ 20 Gy; doses to the liver, no more than 67% of the liver should receive ≥ 20 Gy and no more than 50% of the liver should receive ≥ 30 Gy.

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Toxicity assessment. Patients were observed weekly during the treatment to monitor toxicity. It was graded according to the National Cancer Institute Common Toxicity Criteria (version 2.0). Late toxicity was graded according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer late radiation morbidity scoring scheme.

Follow-up evaluation. The following evaluations were performed until disease progression every 3 months for the first year after the completion of the protocol treatment, every 4 months for the second year, and every 6 months thereafter: physical examination, complete blood count, serum chemistries, gastroscopy with biopsy and CT scan of the abdomen. Endoscopic ultrasound of the stomach and CT scan of the chest were optional.

Response assessment. For the primary tumor in the stomach, complete response (CR) was defined endoscopically as the complete disappearance of all lesions with negative biopsy lasting for ≥ 4 weeks; and progressive disease (PD) was defined as gross tumor progression or the appearance of any new lesion. Non-CR or non-PD was defined as the rest of the CR and PD in evaluable patients. For the involved nodes, responses were judged according to the International Workshop Criteria for non-Hodgkin's lymphoma.[13]

Central pathology review and radiotherapy quality assurance. Formalin-fixed specimens were collected after patient entry and reviewed according to the World Health Organization classification by the central pathology review board of the study. Immunoperoxidase studies were performed on formalin-fixed paraffin sections with the avidin-biotin peroxidase complex method. A panel of monoclonal antibodies against CD3, CD79a, BCL2 (Dako, Santa Fe, CA, USA); and cyclin D1 (clone 5D4, Seto M, Nagoya, Japan) were used.[14] All antibodies were applied after antigen retrieval following microwave oven-heating treatment.

Tumors were considered to be of B-cell origin when the neoplastic cells expressed CD79a and lacked the T-cell-associated marker (CD3). Cases were classified as BCL2-expressing if the protein was detected in more than 50% of tumor cells.

All radiation simulation films, port films and RT charts were reviewed, and protocol compliance was judged in terms of field border placement, dose fractionation and dose constraint to risk organs by the radiation oncology study chair (Satoshi Ishikura).

Statistics. The primary end-point of the present study was tolerability of the treatment based on the incidence of critical toxicities defined as follows: treatment-related death, grade 4 non-hematological toxicity, gastric hemorrhage and/or perforation requiring surgery and unexpected serious adverse event. The sample size was determined to ensure that the true proportion who suffer critical toxicity does not exceed the clinically acceptable range. If two of the 50 cases show the toxicity, the upper 95 and 90% confidence limits would be 13.7 and 12.1%, respectively, and the treatment would be judged as acceptable. Taking into account that 10% of the patients may be ineligible, the total sample size was determined to be 55. Survival was measured from the first day of treatment. Death from any cause was included as an event in the overall survival, and any failure and any cause of death were included as events in the progression-free survival. The overall and the progression-free survival curves were calculated using the Kaplan–Meier method.

Results

Patient population. From December 1999 to February 2003, 55 patients were enrolled. Three patients were judged as ineligible by central pathology review (leiomyosarcoma, 1; senile Epstein–Barr virus-positive B-cell lymphoproliferative disorder, 1; and MALT lymphoma, 1) and the remaining 52 eligible patients were included in the present analysis. Their median age was 61 years (range, 20–73 years), 28 patients were men and 24 patients were women. All cases were immunohistochemically positive for CD79a, but not CD3 or cyclin D1. Ten of the 52 (19%) cases were accompanied by a component of low-grade B-cell MALT lymphoma. The expression of BCL2 was detected in 19 of the 43 (44%) cases examined. Patients and tumor characteristics are summarized in Table 1.

Treatment compliance and toxicity. All 52 eligible patients completed three cycles of CHOP; five patients required dose modification and seven patients required treatment delay ≥ 7 days. RT began 62–92 days (median, 72 days) after the initiation of CHOP. All but one patient, who suffered disease progression, completed the planned RT within 37–43 days (median, 39 days). Common grade 3 or greater acute toxicities during CHOP therapy were leukopenia, 39 (71%); thrombocytopenia, five (9%); nausea, two (4%); and elevation of ALT, three (5%). Grade 3 or greater acute toxicities during RT were leukopenia, four (8%); thrombocytopenia, two (4%); and elevation of ALT, one (2%). No critical toxicity, including massive hemorrhage or perforation of the stomach, was observed in the 52 eligible patients, and the probability of the true proportion who suffer critical toxicity exceeding 0.056 was less than 5%. As of the date of this analysis, we observed compression fracture of the irradiated thoracic spine in two patients as late adverse events after the treatment. Otherwise there was no grade ≥ 3 late adverse event.

Protocol compliance of radiotherapy. In 44 of the 52 cases, complete radiation therapy information was available for review at the time of the analysis. Twenty-three of 44 cases (52%) were judged per protocol, 17 (39%) were acceptable deviations

Table 1. Patient and tumor characteristics

	No.
Eligible patients	52
Age (years)	
median	61
range	20–73
Gender	
male	28
female	24
Performance status	
0	37
1	15
Clinical stage	
I	36
II_1	16
IPI	
low	47
low–intermediate	5
Location	
upper	6
middle	36
lower	10
No. lesions	
solitary	32
multiple	20
Tumor types	
superficial and depressed	9
protruding	6
ulcerative	36
others	1
Depth of invasion	
mucosa	2
submucosa	4
muscularis propria	24
subserosa	18
penetrates serosa	4

IPI, International Prognostic Index.

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