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.

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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

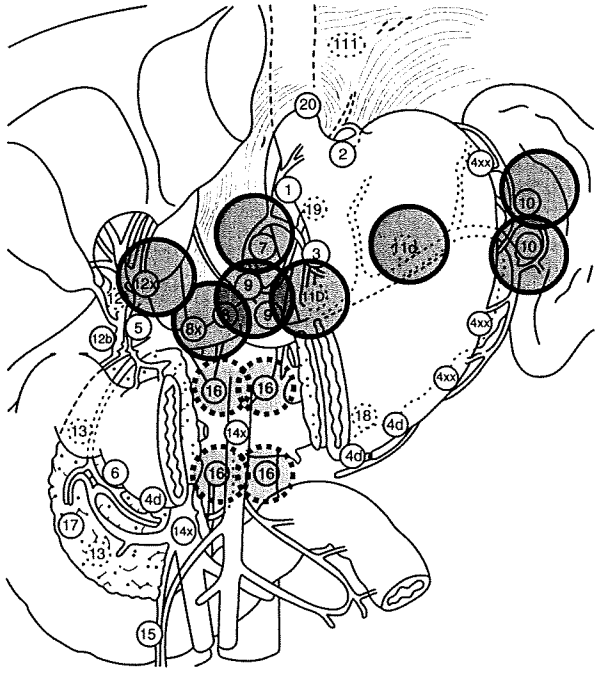

Fig. 1 Definitions of bulky N2 and para-aortic nodal metastases. Bulky N2 (in solid circles): at least one node of 3 cm or more in diameter, or at least three consecutive nodes each of diameter 1·5 cm or more, along the coeliac, splenic, common or proper hepatic arteries. Para-aortic nodes (in dashed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

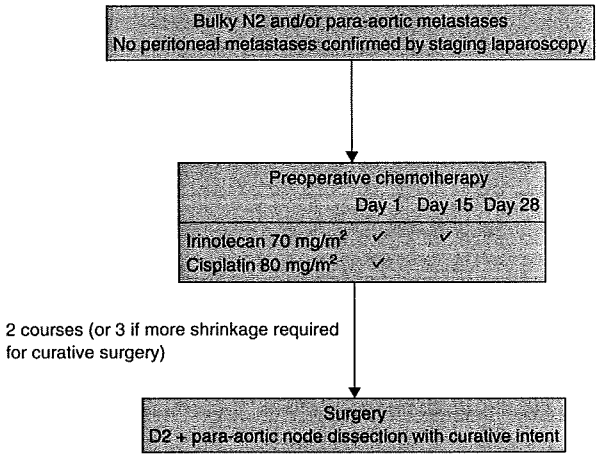

Fig. 2 Study outline

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.

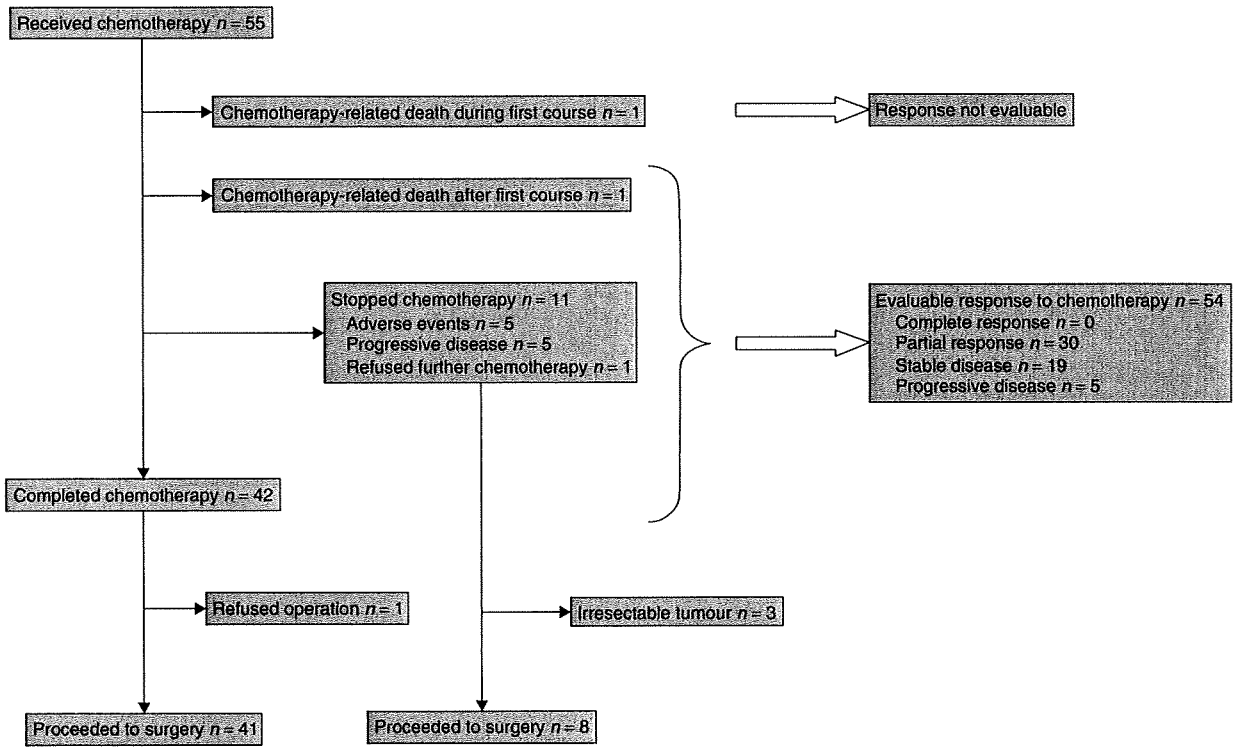

Fig. 3 Flow diagram from chemotherapy to surgery in 55 eligible patients

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.

Surgical findings and surgical pathology

Forty-nine patients proceeded to surgery (*Table 2*). Resection with curative intent was undertaken in 46 patients. One patient had only exploratory laparotomy because of peritoneal metastases, one underwent gastrojejunostomy, and one required palliative resection to stop bleeding from the primary tumour. Of the 46 patients who had resection with curative intent, R0 resection was performed in 36, R1 in four (positive surgical margin, three; positive peritoneal cytology, one) and R2 in six with unresectable tumours (*Table 3*). Thus, the proportion of R0 resections in the 55 eligible patients was 65 (95 per cent c.i. 51 to 78) per cent.

The pathological response rate in resected patients was 15 (95 per cent c.i. 7 to 27) per cent.

Adverse events from chemotherapy

Toxicity of grade 3 or above included leucopenia (31 per cent), neutropenia (55 per cent), anaemia (24 per cent), febrile neutropenia (16 per cent), nausea (36 per cent), vomiting (13 per cent) and diarrhoea (5 per cent). Two patients died from myelosuppression after the initial chemotherapy course, giving a chemotherapy-related mortality rate of 4 per cent (two of 55 patients).

Surgical complications

Surgical complications are shown in *Table 4*. One (2 per cent) of 49 patients died from multiple organ failure 3 days after thoracoabdominal surgery for oesophageal invasion in addition to a total gastrectomy with pancreaticosplenectomy.

Overall survival

The 3-year survival rate was 27 (95 per cent c.i. 15 to 39) per cent, and thus the lower limit of the 95 per cent c.i. was higher than the prespecified threshold (*Fig. 4*). Median survival was 14·6 (95 per cent c.i. 10·1 to 24·1) months.

Table 4 Surgical complications in the 49 operated patients

	No. of patients
Leakage	1 (2)
Pancreatic fistula	6 (12)
Abdominal abscess	2 (4)
Pneumonia	2 (4)
Ileus	0 (0)
Wound infection	2 (4)
Stenosis of anastomosis	1 (2)
Cardiac failure	1 (2)
Renal dysfunction	1 (2)
Other	6 (12)

Values in parentheses are percentages.

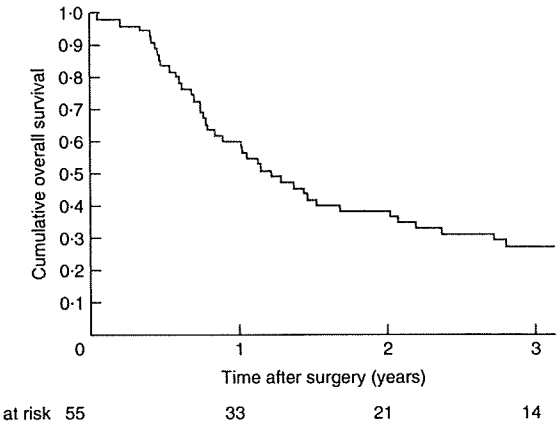

Fig. 4 Kaplan–Meier overall survival curve for the 55 eligible patients

Discussion

This multi-institutional phase II prospective trial of neoadjuvant chemotherapy in locally advanced gastric cancer with extensive lymph node metastases showed that multimodality treatment can achieve a high 3-year survival rate of 27 per cent. Usually these patients rarely survive for more than 3 years when treated by chemotherapy alone or by surgery followed by postoperative chemotherapy. Thus, the protocol treatment was effective for these patients, but was achieved at the cost of considerable morbidity and mortality, and the study had to be stopped prematurely because of treatment-related deaths.

The combination chemotherapy of irinotecan plus cisplatin was chosen because it had achieved a high response rate of 59 per cent in a previous phase II study of chemotherapy-naive patients with metastatic gastric cancer[11]. At the start of the present study in 2000, this was considered to be the most effective and promising regimen for gastric cancer. In Japan, based on these data, a phase III trial was initiated to determine the superiority of irinotecan plus cisplatin compared with 5-fluorouracil (5-FU) alone for metastatic gastric cancer[17]. In the present study, the clinical response to preoperative chemotherapy was 55 per cent, comparable with previous results using this regimen in patients with metastatic gastric cancer[11]. Although the above-mentioned Japanese phase III trial (JCOG 9912) did not demonstrate superiority for this regimen compared with 5-FU alone, a subset analysis for tumours with target lesion defined by RECIST

showed that combination chemotherapy of irinotecan plus cisplatin gave a median survival of 12·1 months, which was significantly longer than for 5-FU alone[17]. This suggested that irinotecan plus cisplatin was especially active against tumours forming bulky masses[17]. In contrast to the impressive clinical response of metastatic nodes, the pathological response in the primary tumours was relatively low in the present study. In gastric cancer, the pathological response rate is usually less than 20 per cent for any chemotherapeutic regimen, suggesting the importance of appropriate local control by surgery. The relatively good overall survival at 3 years in the present study appears to be due to the effects of neoadjuvant chemotherapy in two ways: downstaging of lymph node metastases, which enabled R0 resection in 65 per cent of patients, and good control of micrometastases.

Treatment-related death was observed in 5 per cent of patients in this study, indicating that this treatment protocol is hazardous. Of three patients, two died from chemotherapy-induced myelosuppression. Neutropenia and diarrhoea were the major toxicities of this regimen, as reported previously[11,17]. Compared with these trials, toxicity in the present study was relatively low, but the mortality rate was high. In two treatment-related deaths from chemotherapy, severe myelosuppression appeared immediately after the first administration of irinotecan plus cisplatin. Boku and colleagues[17] observed severe diarrhoea only during the first course of the same regimen in patients with unresectable gastric cancer. Noda and co-workers[18] reported on the efficacy of combination therapy with irinotecan plus cisplatin for small cell lung cancer, using a different schedule and dosage than those in the present study. They observed treatment-related deaths in three patients (4 per cent) during the first or second cycle of chemotherapy. Taken together, all of these results indicate that severe haematological toxicity and diarrhoea should be managed carefully, especially during the initial cycles of chemotherapy.

Recently, genetic polymorphism of UTG1A1, which is involved in glucuronidation of SN-38 or is an active metabolite of irinotecan, has been reported to be associated with irinotecan toxicity[19,20]. Polymorphisms of UGT have also recently been suggested as a risk factor for irinotecan-induced neutropenia[21]. These factors might have been involved in the treatment-related deaths observed in the present study, although genetic analysis was not performed. Patient risk may be reduced not only by careful management of myelosuppression, but possibly also by patient selection based on genetic analysis. However, further studies are needed to confirm this. Because the combination chemotherapy regimen employed in this study is difficult to manage in terms of toxicity, a new phase II study has been initiated to evaluate a preoperative S-1 (oral anticancer drug that combines tegafur, a prodrug of fluorouracil, with 5-chloro-2,4-dihydropyrimidine and potassium oxonate) plus cisplatin regimen, which is considered less toxic for patients with extensive nodal metastases. S-1 and cisplatin showed a high response rate of over 50 per cent with mild toxicity in recent trials of patients with metastatic gastric cancer[22,23].

The operative mortality rate in this study was 2 per cent. In the JCOG 9501 trial, which compared D2 with D2 plus para-aortic nodal dissection, the mortality rate was 0·8 per cent for D2 plus para-aortic nodal dissection[13], whereas in the JCOG 9502 trial, which compared an abdominal approach with a left thoracoabdominal approach for gastric tumours invading the oesophagus, mortality rates were 0 and 4 per cent respectively[24]. Thus, the thoracoabdominal approach was the more hazardous of the two procedures. Because the influence of preoperative chemotherapy on surgery is unclear, patients who require such an extensive thoracoabdominal operation should probably be excluded from future studies.

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The authors declare no conflict of interest.

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