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Significance of Lavage Cytology in Advanced Gastric Cancer Patients

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Abstract
Background Lavage cytology positive (Cy1) is well known as a poor prognostic factor in advanced gastric cancer patients. However, the optimal therapeutic strategy for patients with Cy1 has not yet been established. The aim of this study was to evaluate the clinical significance of Cy1 for the purpose of establishing a suitable therapeutic strategy.
Methods The data of 996 consecutive advanced gastric cancer patients who underwent gastrectomy between 1992 and 1998 at the National Cancer Center Hospital were retrospectively studied.
Results The 2- and 5-year survival rates of the patients who underwent gastrectomy without any other noncurative factors besides Cy1 were 25.3 and 7.8%, respectively. When the analysis was limited to type 4 advanced gastric cancer patients, none of the patients with Cy1 survived for more than 40 months.
Conclusions The prognosis of gastric cancer patients with Cy1 is very poor. Some patients show long survival after standard gastrectomy with D2 lymph node dissection; however, the prognosis of type 4 gastric cancer patients with Cy1 is so poor that multimodality therapy, including perioperative chemotherapy, is essential.

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Introduction

Recently, standard therapeutic strategies have been established for gastric cancer patients based on the results of some clinical trials [1–3]. The treatment outcomes of early gastric cancer patients are now favorable [4] due to the remarkable progress in endoscopic treatments [5, 6] and minimally invasive surgery, including function-preserving gastrectomy [7] and laparoscopic gastrectomy [8]. However, many surgeons believe that the treatment outcomes of advanced gastric cancer patients remain poor.

Peritoneal dissemination is one of the most frequent modes of metastasis in advanced gastric cancer. The possibility of cure in patients with this metastasis is considered to be low because no effective curative therapy has been established so far. Even after curative surgery in patients without evidence of peritoneal dissemination at the time of the operation, many patients develop peritoneal recurrence, which is extremely difficult to overcome [9].

The majority of patients showing lavage cytology-positive (Cy1) intraoperatively develop peritoneal recurrence [9]. Cy1 can be interpreted as a state in which free cancer cells are floating in the abdominal cavity, with small peritoneal foci already established in the peritoneum [10]. However, despite Cy1 being recognized as a definite predictive factor for peritoneal recurrence of gastric cancer[11–13], no effective treatment strategies have been established for Cy1 gastric cancer patients. In some cases prolonged survival has been achieved, even in Cy1 patients. When the analysis is limited to patients with type

4 advanced gastric cancer, however, the prognosis of Cy1 seems to be particularly severe [14].

In this study, the exact relevance of Cy1 and the clinical outcomes of these patients were evaluated based on data from a large-volume center of gastric cancer patients. This is expected to be helpful for developing a suitable new therapeutic strategy for this condition.

Patients and methods

The data of 996 consecutive patients who underwent gastrectomy between 1992 and 1998 for advanced gastric cancer that invaded the gastric wall deeper than the muscularis propria, as assessed by histopathological examination performed after the surgery at the National Cancer Center Hospital, were studied retrospectively. All patients underwent partial or total gastrectomy with lymph node dissection. Basically, patients with peritoneal dissemination underwent simple gastrectomy with minimum dissection; other patients underwent standard dissection. Patients with preoperative, clinically definitive peritoneal dissemination, i.e., ascites, hydronephrosis, and colonic stenosis by barium enema study, were not included in this study. Both the patients with diffuse peritoneal dissemination detected at surgery and those with locally resectable peritoneal dissemination were included in this study.

The former Japanese Classification of Gastric Carcinoma defined peritoneal dissemination as P0, P1, P2, and P3 according to its extent, while the current classification (13th) is P0 and P1: with or without. All patients were classified according to the Japanese Classification of Gastric Carcinoma. Macroscopic features of advanced gastric cancer are classified as type 0: superficial, flat tumors; type 1: polypoid tumors; type 2: ulcerated tumors; type 3: ulcerated tumors without definite limits; type 4: diffusely infiltrating carcinomas; and type 5: nonclassifiable carcinomas. For the purpose of the present analysis, the patients were divided into two groups based on the macroscopic features of type 4 gastric cancer and others.

Cytopathology

Cytological samples were obtained just after laparotomy. Approximately 100 ml of sterile saline was instilled into the pouch of Douglas and then aspirated. The samples were subjected to cytocentrifugation onto slide glasses at 1700 rpm for 60 s at room temperature. The slides were then fixed in 95% ethanol, followed by Papanicolaou and alcian blue stains. Additional slides were stained immunocytochemically for CEA (Mochida, CEA010,Tokyo, Japan), and also for epithelial antigen using the BerEP4 antibody (DAKOPATTS, Glostrup, Denmark). Two to three cytotechnologists and cytopathologists independently examined all the slides to arrive at a diagnosis by consensus. A patient was considered to have positive peritoneal cytology (Cy1) if adenocarcinoma cells were detected, regardless of the number of cells. In cases where atypical cells were present but could not be definitely identified as cancer cells, the peritoneal cytology was estimated as class 3, or indeterminate. Basically, lavage cytology was carried out intraoperatively for advanced gastric cancer cases. The data of cytology in this article, recorded in our database, is the final result confirmed by immunohistochemistry several days after surgery.

Statistical analysis

Statistical analysis was carried out using SPSS software version 11.5 (SPSS Inc., Chicago, IL). The Kaplan–Meier method was used for constructing the survival curves, and the log-rank test was used for evaluating the statistical significance of differences between the survival curves.

Results

Among the 996 cases included in our study, cytological examination was performed in 779 (Table 1). Cytological examination was positive for cancer cells mainly in advanced gastric cancer patients in whom the tumor had invaded outside the serosal surface (T3) or directly invaded adjacent organs (T4) (Table 1).

As expected, many of the patients with peritoneal dissemination (P1) were cytology-positive (Cy1) but 27 patients with peritoneal dissemination (P1) were cytology-negative (Cy0) (Table 2).

Among the 996 consecutive patients, 217 patients who did not undergo cytological examination and 13 whose cytological examination revealed an indeterminate result were excluded from the analysis; in addition, 65 patients who had distant metastasis to the liver, lung, and supraclavicular lymph nodes were also excluded. The remaining

Table 1 Correlation between cytological examination and the depth of the tumors

	T2 (MP)	T2 (SS)	T3	T4	Total
Cy0	78	156	251	56	541
Cy1	1	5	137	82	225
Indeterminate	0	0	9	4	12
Undone	105	58	44	10	217
	184	219	441	152	996

MP muscularis propria, *SS* subserosa, *Cy0* cytology-negative, *Cy1* cytology-positive

Table 2 Correlation between the results of cytological examination and presence/absence of peritoneal dissemination

	P0	P1	Total
Cy0	514	27	541
Cy1	101	124	225
Indeterminate	8	5	13
Undone	196	21	217
	819	177	996

P0 without peritoneal dissemination, *P1* with peritoneal dissemination, *Cy0* cytology-negative, *Cy1* cytology-positive

Table 3 Number of patients per peritoneal dissemination and cytology type of tumors

	Type4	Other Types	Total
P0Cy0	53	432	485
P0Cy1	33	55	88
P1Cy0	9	13	22
P1Cy1	61	45	106
	156	545	701

P0 without peritoneal dissemination, *P1* with peritoneal dissemination, *Cy0* cytology-negative, *Cy1* cytology-positive

701 patients were divided into four groups: (1) peritoneal dissemination-negative and cytology-negative (P0Cy0), (2) peritoneal dissemination-negative and cytology-positive (P0Cy1), (3) peritoneal dissemination-positive and cytology-negative (P1Cy0), and (4) peritoneal dissemination-positive and cytology-positive (P1Cy1). The number of patients in each category is given in Table 3.

Survival

The overall survival curves of the four groups are shown in Fig. 1. The prognosis of the patients with P1 and/or Cy1 was worse than that of the patients with P0Cy0. The prognosis of the P0Cy1 patients was better than that of the P1Cy1 patients ($p = 0.0002$, log-rank). The median survival time of the P0Cy1 patients was 12 months. The 2-year and 5-year survival rates in the P0Cy1 patients were 25.3% (95% confidence interval [CI] = 16.2–34.4%), and 7.8% (95% CI = 2.0–13.5%) (Table 4). Five (5.7%) of the 88 P0Cy1 patients survived for more than 5 years without evidence of recurrent disease.

The 88 P0Cy1 patients consisted of 33 patients with type4 gastric cancer and 55 with other types of gastric cancer. The survival of P0Cy1 patients with type 4 gastric cancer was significantly worse than that of the patients with other types of gastric cancer, as shown in Fig. 2 ($p = 0.0072$, log-rank). The median survival time was 10 months. The 2-year survival rate was 12.1% (95% CI = 0.12–22.1%) (Table 4). None of the patients survived for more than 40 months. Among the 88 P0Cy1 patients, 51 patients received postoperative adjuvant chemotherapy, mainly based on fluorouracil, while 35 did not, although this was not randomized. There was no information about adjuvant therapy for two patients who had moved to other hospitals soon after surgery. There was no significant difference in the survival curves between the P0Cy1 patients who received and did not receive adjuvant chemotherapy ($p = 0.1238$, log-rank) (Fig. 3).

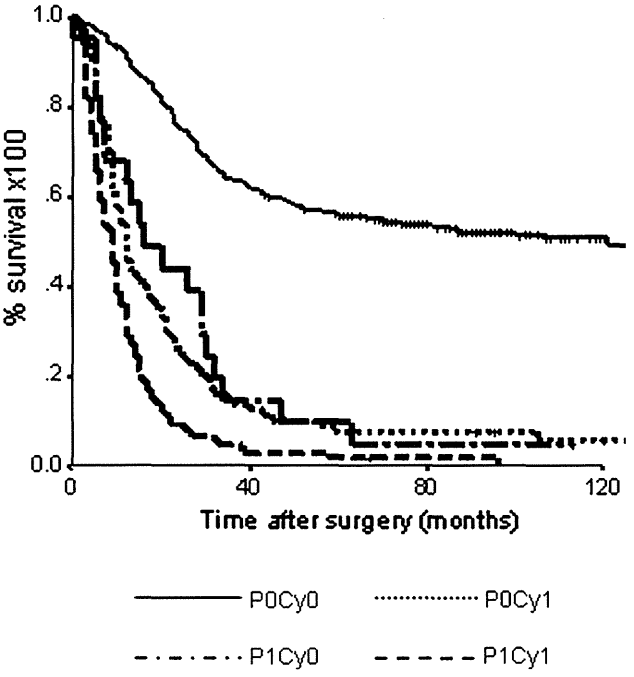

Fig. 1 Overall survival curves of gastric cancer patients (P0Cy0, P0Cy1, P1Cy0, and P1Cy1) are shown. The survival of P0Cy1 patients was poor but better than that of P1Cy1 patients ($p = 0.0002$)

Discussion

Lavage cytology-positive (Cy1) is most commonly encountered among gastric cancer patients with deeply invading tumors that extend outside the gastric wall [9, 15]; therefore, it is thought that the cancer cells escape from the surface of the tumors into the intraperitoneal cavity [16]. This is not clearly supported by some experiments, but Cy1 may reflect systemic spread of the tumor cells via the lymphatic pathway, which can cause retroperitoneal invasion, hydronephrosis, and rectal stenosis [17].

The prognosis of the patients who are found at the time of surgery to show peritoneal dissemination is expectedly very poor. The indication of mass reductive or palliative surgery should be evaluated by clinical trial [18], but it is regarded, by consensus, that gastric cancer patients with

Table 4 Survival rate and median survival time of POCy1 gastric cancer patients per type of tumor

	1 year	2 years	3 years	5 years	MST
POCy1					
All ($n = 88$)	46.0 (35.5–56.5)	25.3 (16.2–34.4)	13.8 (6.5–21.0)	7.8 (2.0–13.5)	12 (9.7–14.3)
Type 4 ($n = 33$)	45.5 (28.5–62.4)	12.1 (0.1–22.1)	0	0	10 (6.8–13.2)
Others ($n = 55$)	51.9 (38.5–65.2)	33.3 (20.8–45.9)	22.2 (11.1–33.3)	12.5 (3.5–21.5)	13 (7.6–18.4)

MST median survival time in months (95% confidence interval)

Values are % (95% confidence interval)

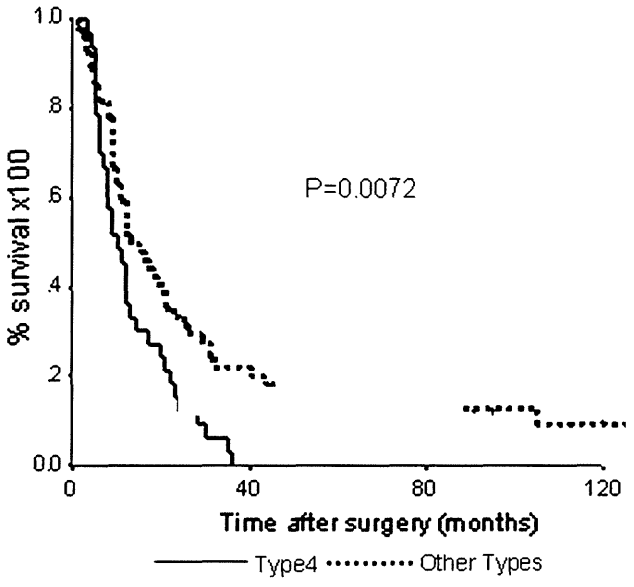

Fig. 2 The survival of POCy1 patients with type 4 advanced gastric cancer was significantly worse than that of patients with other types of advanced gastric cancer ($p = 0.0072$)

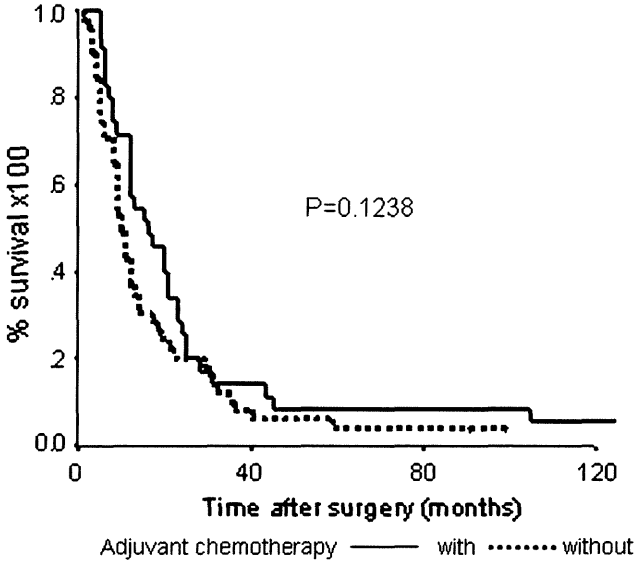

Fig. 3 There was no significant difference in the survival curves between POCy1 patients treated/not treated by adjuvant chemotherapy ($p = 0.1238$)

definite peritoneal dissemination are not suitable candidates for gastrectomy.

Cytological examination of intraperitoneal lavage fluid is performed in many institutions in Japan. In some institutions the result is confirmed intraoperatively, while in others it is confirmed on the following day. Cy1 is now included as one of the factors defining Stage IV in the Japanese classification of gastric carcinoma [19] because the prognosis of these patients with Cy1 is poor. However, the knowledge of a patient being Cy1 alone does not seem to be sufficient to decide on the therapeutic procedure [20]. The current consensus is that gastric cancer patients with intraoperatively confirmed Cy1 undergo standard gastrectomy and postoperative adjuvant chemotherapy [21]. Extended lymph node dissection and resection of other organs have gradually become less frequent in these patients. The efficacy of adjuvant chemotherapy with S-1 (1 M tegafur-0.4 M gimestat-1 M otastat potassium) after curative surgery has been reported [3]; however, no satisfactory postoperative adjuvant chemotherapy regimen for gastric cancer patients with Cy1 has been established. In our study, adjuvant chemotherapy using agents other than S-1 yielded no survival benefit. At our institution, S-1 was given as adjuvant chemotherapy to the patients, mainly after the end of the study period. In a future article we shall report on the efficacy of adjuvant chemotherapy with S-1 in gastric cancer patients with Cy1 compared with that in the subjects of this study as the historical control.

In this study, the 5-year survival rate of gastric cancer patients with POCy1 was 7.8%. This poor result must be interpreted as suggesting that previously used treatment, including surgery alone, was not suitable for these patients [22]. If those patients undergo surgery first, more intensive adjuvant chemotherapy would be needed. Currently, S-1 is given to these patients as adjuvant therapy [21, 23], but is S-1 monotherapy sufficient? A feasibility study of S-1 plus platinum as adjuvant therapy is ongoing (data not published); however, compliance with this therapy may not be favorable due to the unstable postoperative status of the gastric cancer patients. It is quite natural to expect that preoperative chemotherapy might be useful for those patients [24].

In order to carry out preoperative chemotherapy, information on Cy1 must be confirmed by staging laparoscopy [25]. In Japan, staging laparoscopy has been popular, but it may be difficult for it to be routinely performed in every advanced gastric cancer patient at every institution. Definitive evidence on the efficacy of preoperative chemotherapy, such as that from the MAGIC trial [26], is mandatory for encouraging the use of this therapy in Japan.

When only type 4 advanced gastric cancer patients are included in the analysis, the prognosis of those with Cy1 is extremely poor. No patient survived for more than 40 months after surgery in this study. The survival curve of the patients with P0Cy1 was almost the same as that of the patients who were found to have peritoneal dissemination (P1Cy1) at the time of the surgery (data not shown). The indication for gastrectomy for these patients must be discussed [27]. No surgeon performs gastrectomy for linitis plastica with peritoneal dissemination, except for palliating stenosis or bleeding. The former therapeutic strategy of immediate surgery and adjuvant chemotherapy has a less curative power for these patients with such a poor prognosis, and preoperative chemotherapy should be tried. Controlled arm may be the chemotherapy without surgery [28]. Information on Cy1 is necessary for determining the therapeutic strategy in patients with type 4 advanced gastric cancer, therefore, staging laparoscopy must be carried out first.

The patients with peritoneal dissemination are not always cytology-positive. The survival of P1Cy0 patients is better than that of P1Cy1 patients (Fig. 1) ($P = 0.0028$, log-rank). When the analysis is limited to type 4 gastric cancer, the survival of P1Cy0 patients is also better than that of P0Cy1 and P1Cy1patients (not shown), but the sample size (P1Cy0: $n = 9$) is too small for statistical evaluation. The P1Cy0 patients with local disseminated nodules may be the subset that can benefit from intraoperative chemotherapy.

In conclusion, curative treatment has been scarce for gastric cancer patients with Cy1 until now. The prognostic benefit of adjuvant chemotherapy with S-1 has been expected for years, but more intensive adjuvant chemotherapy, preoperative chemotherapy, and intraperitoneal chemotherapy [29] also warrant trials. The prognosis of type 4 gastric cancer patients with Cy1 is especially poor; therefore, it is recommended that such patients be treated at large-volume institutions with new therapeutic strategies developed based on clinical trials.

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A phase II study of preoperative chemotherapy with S-1 plus cisplatin followed by D2/D3 gastrectomy for clinically serosa-positive gastric cancer (JACCRO GC-01 study)

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Abstract

Aims: Clinically serosa-positive (T3–4) gastric cancer has a poor prognosis. This phase II trial explored the feasibility and safety of preoperative chemotherapy followed by D2 or D3 gastrectomy in this type of gastric cancer.
Methods: Patients with T3–4 gastric cancer received one course of S-1 (80 mg/m^2 daily for 3 weeks) and cisplatin (60 mg/m^2 on day 8) chemotherapy and then underwent D2 or D3 gastrectomy with curative intent. Primary endpoint was toxicities.
Results: Of 50 patients enrolled, 49 were eligible and received the treatment protocol. Chemotherapy-related toxicities were mild; grade 3 neutropenia in 2 patients, anorexia in 3, and nausea in 2, and no grade 4 toxicities. Clinical response was achieved in 13 of 34 evaluable patients. Of the 49 patients, 39 underwent D2 or D3 dissection. There was no surgical mortality. Operative morbidity occurred in 5 of 49 patients, including pancreatic fistula in 1 and abdominal abscess in 2.
Conclusion: This multi-modality treatment seems to be feasible and safe for T3–4 gastric cancer.

Keywords: Gastric cancer; Chemotherapy; Surgery; Phase II

Introduction

Gastric cancer remains the second leading cause of cancer death in the world and is the most frequent malignancy in Japan, South America, and Eastern Europe.[1] Complete resection is essential for cure,[2] and because more than half of T3 and T4 tumors have metastasized to lymph nodes along the major branch arteries or in the para-aortic area, complete resection has involved D2 or D3 dissection in Japan.[3,4] However, despite resection of these tumors with curative intent, prognosis has been limited.[5] To improve the survival of these patients, new treatment strategies must be developed.

Most clinical trials of postoperative adjuvant chemotherapy have failed to prove a survival benefit.[6] However, a large phase III trial recently demonstrated that adjuvant chemotherapy with S-1 (1 M tegafur–0.4 M gimestat–1 M ostat potassium) significantly improved survival after D2 curative

Abbreviations: CF, 5-FU plus cisplatin; ECF, triplet chemotherapy of CF plus epirubicin; DCF, CF plus docetaxel; JACCRO, Japan Clinical Cancer Research Organization; WBC, white blood cell count; PLT, platelet count; GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; ALP, alkaline phosphatase; RECIST, response evaluation criteria in solid tumors; JCOG, Japan Clinical Oncology Group.

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gastrectomy in Japanese patients with T2N+ or T3 disease.[7] Based on this, D2 surgery and postoperative S-1 chemotherapy has been established as a standard treatment in Japan. Nonetheless, even with adjuvant S-1 chemotherapy, the prognosis for T3 tumors was not satisfactory.

Preoperative chemotherapy followed by extended surgery has some theoretical benefits when compared with postoperative chemotherapy.[8] If bulky tumors are reduced in size by chemotherapy, complete tumor removal could theoretically be easily achieved by extended surgery. If distant micrometastases are eliminated by chemotherapy, complete resection by extended surgery may improve survival and result in cure in some cases. However, preoperative chemotherapy followed by extended surgery has not been confirmed in phase III trial.

A high response rate and relatively low toxicity are required for preoperative chemotherapy, because target tumors are resectable or marginally resectable and the patients must receive potentially curative surgery after chemotherapy. Combined chemotherapy with S-1 plus cisplatin is an attractive regimen for preoperative chemotherapy for gastric cancer. A previous phase II trial of this regimen in metastatic gastric cancer reported a high response rate of 76% and acceptable toxicities.[9] Recently, a Japanese phase III trial of chemotherapeutic regimens for metastatic gastric cancer (SPIRITS trial) demonstrated that S-1 plus cisplatin led to significantly longer median overall survival than S-1 alone (13 months vs. 11 months).[10] Moreover, in the recent international phase III trial (FLAGS), S-1 plus cisplatin had lower toxicity but achieved equally overall survival compared with 5-FU plus cisplatin (CF) (Ajani JA, et al. presented at the 2009 Gastrointestinal Cancers Symposium). Triplet chemotherapy of CF plus epirubicin (ECF) or CF plus docetaxel (DCF) is effective but more toxic than CF.[11]

However, the influence of preoperative chemotherapy on D2 or D3 surgery has not been fully evaluated, although D2 and D3 gastrectomy are safe procedures in Japan.[12] Unlike D0 or D1 surgery, D2 or D3 gastrectomy involves nodal dissection along the pancreas, which can cause pancreatic fistula or abdominal abscess. These complications can be lethal and might be increased by preoperative chemotherapy. The effect of preoperative chemotherapy on surgical mortality or morbidity with these procedures has not been fully clarified. Recently, preoperative chemotherapy of CPT-11 plus cisplatin followed by D3 dissection was tested in phase II trial to evaluate the efficacy and toxicity in Japan.[13] However, this trial has been terminated due to high treatment-related death during the accrual. A safe and effective regimen before extended surgery has yet to be reported.

The Japan Clinical Cancer Research Organization (JACCRO) therefore, conducted a multi-institutional phase II trial (JACCRO GC-01) to evaluate the feasibility and safety of preoperative chemotherapy with S-1 plus cisplatin followed by curative D2 or D3 gastrectomy for clinically serosa-positive (T3–4) gastric cancer.

Patients and methods

Eligibility criteria

Eligibility criteria were: (1) histologically proven gastric adenocarcinoma; (2) stage clinically assessed as T3–4, N0–N3 which is classified according to 2nd English Edition of Japanese Classification of Gastric Carcinoma,[14] and M0; (3) age 20–75 years; (4) Eastern cooperative oncology group (ECOG) performance status 0–1; (5) no prior therapy; (6) sufficient organ function [white blood cell count (WBC) 4000–12,000 mm^3, platelet count (PLT) >100,000/mm^3, glutamic oxaloacetic transaminase (GOT) <80 IU/l, glutamic pyruvic transaminase (GPT) <80 IU/l, total bilirubin <1.5 mg/dl, alkaline phosphatase (ALP) < two times greater than upper limit of normal, creatinine <1.2 mg/dl, creatinine clearance >60 ml/min, and hemoglobin >8.0 g/dl]; and (7) written informed consent. Clinical diagnosis was based on gastric fiberscopy, upper gastrointestinal series, computed tomography, and ultrasonography. Serosal invasion of the primary tumor was evaluated by computed tomography. Endoscopic ultrasonography or diagnostic laparoscopy was not mandatory, because these remain outside of routine preoperative examinations in Japan. Exclusion criteria were (1) severe co-morbidities; (2) active and acute bleeding from the digestive tract; (3) insufficient oral intake; (4) synchronous or previous malignancy other than carcinoma *in situ*; and (5) contraindications to S-1 or cisplatin. All patients provided informed consent before registration and were registered centrally at the JACCRO Data Center by means of the online Flexible licence assisted data server (FLADS) system. The JACCRO Data Center conducted the data management, central monitoring, and statistical analysis.

Preoperative chemotherapy

On the basis of previous reports S-1 (80 mg/m^2) was given orally every day for 3 weeks and cisplatin (60 mg/m^2) was administered intravenously on day 8 as one course.[9,10] If the patient had a WBC of 2000/mm^3 or lower, neutrophil count of 1000/mm^3 or lower, PLT of 75,000/mm^3 or lower, diarrhea or mucositis of grade 3 or higher, GOT or GPT of grade 2, or serum creatinine of grade 1, chemotherapy was postponed until recovery from these adverse events and the next dose of S-1 was reduced to 70 mg/mm^2. For diarrhea or mucositis of grade 1, chemotherapy was postponed until recovery. In the case of GOT and/or GPT of grade 3 or higher or serum creatinine of grade 2 or higher, chemotherapy was terminated. If the patient had cardiac or neurologic toxicities, chemotherapy was postponed until recovery from these toxic effects and confirmation of their cause. For any other adverse events of grade 2 or higher, chemotherapy was postponed until recovery. If the chemotherapy was postponed but the toxicities had not resolved within 21 days, the chemotherapy was terminated after this period.

Surgery

Tumor resectability was assessed after completion of chemotherapy. Resection criteria were (1) R0 resection was anticipated by D2 or extended D2 gastrectomy; (2) sufficient organ function (WBC $>3000/mm^3$, neutrophils $>1000/mm^3$, PLT $>100{,}000/mm^3$, GOT <100 IU/l, GPT <100 IU/l, creatinine <1.5 mg/dl); and (3) no active infection. Patients who fulfilled these criteria were treated by D2 or D3 gastrectomy with curative intent between two and four weeks after finishing chemotherapy. The precise procedure of D2 and D3 dissection has been reported previously.[12,15] Combined resections of adjacent organs were permitted when these procedures were indispensable for curative resection.

Treatment defined by the protocol

The treatment protocol was defined as completed when a patient received preoperative chemotherapy and underwent R0 resection by gastrectomy with D2 or D3 dissection. The treatment protocol was stopped when: (1) response was evaluated as progressive disease during chemotherapy; (2) the patient did not meet the criteria for surgery after chemotherapy; (3) the patient underwent surgery after chemotherapy but this took the form of exploratory laparotomy, bypass, or non-R0 resection; (4) the patient refused further participation; or (5) the doctor recommended stopping the protocol. After the treatment protocol was stopped, any treatment was allowed and postoperative adjuvant therapy was not defined.

Endpoints

Primary endpoint was toxicities. Secondary endpoints included response rate and overall survival.

Evaluation

The response rate was evaluated only in patients with measurable lesions; Response Evaluation Criteria in Solid Tumors (RECIST) criteria were used[16] and response to chemotherapy was evaluated by external review committee. Adverse reactions during chemotherapy were evaluated by National Cancer Institute – Common Toxicity Criteria Version 2.0.[17]

Statistical hypothesis

As it is difficult to predict the occurrence of severe adverse events or treatment-related deaths and to calculate sample size, feasibility and safety was evaluated in calculated sample size based on the response rate to be required in this setting. A Simon optimal two-stage design[18] was used to calculate the sample size, assuming an anticipated response rate of 50% and a threshold response rate of 30% with 10% alpha error and 10% beta error. Using this design, if at least 8 objective responses were observed among 22 patients in the first stage, an additional 24 patients would be recruited to the second stage. Taking into account tumors without measurable lesions and patients not fulfilling the eligibility criteria, sample size was determined to be 50. Statistical analysis was performed with SAS version 9.1 (SAS Institute, Cary, NC). This phase II trial was approved by the JACCRO Protocol Review Committee and the institutional review board of each of the 8 JACCRO institutions involved.

Results

Patients

Between February 2004 and January 2005, 50 patients were enrolled and the study was terminated. During the accrual, unpredicted severe adverse events or treatment-related death was not observed. One of these patients declined to participate, while the other 49 were eligible and received the treatment protocol. Table 1 shows patient demographics and tumor characteristics. Clinically apparent nodal disease was observed in 40 patients.

Preoperative chemotherapy and toxicities

Of all 49 eligible patients, 3 did not receive cisplatin because of S-1-related toxicity. The average proportion of actual dose to proposed dose was 94% (2219.2 mg/2348.6 mg) for S-1 and 94% for cisplatin (87.8 mg/

Table 1
Patient demographics and pre-treatment tumor characteristics (all eligible patients, $n = 49$).

Age (median, range)	62, 20–73
Sex (male/female)	36/13
PS (0/1)	46/3
Macroscopic type	
1	4
2	6
3	24
4	14
5	1
Histologic type	
Differentiated	17
Undifferentiated	31
Miscellaneous	1
Depth of tumor invasion	
T3	44
T4	5
Nodal status[a]	
N0	9
N1+, perigastric	17
N2+, along major branch arteries	12
N3+, para-aortic	11

[a] Nodal status was classified according to 2nd English Edition of Japanese Classification of Gastric Carcinoma.[14]

92.0 mg). Adverse events during chemotherapy are shown in Table 2. There were no grade 4 and a few grade 3 toxicities.

Clinical response

Clinical response could be evaluated in 34 patients who had enlarged lymph nodes as target lesions as defined by RECIST criteria. There were 13 responders (all showed partial response); 18 patients had stable disease and 3 had progressive disease. Thus, 13 of 34 evaluable patients demonstrated a clinical response (38%) with a 95% confidence interval from 22% to 56%.

Surgery

All of the 49 patients who completed chemotherapy underwent surgery. Surgical findings are shown in Table 3. Three patients underwent exploratory laparotomy due to massive peritoneal dissemination, and 7 underwent palliative D0 or D1 resection due to peritoneal dissemination or extended lymph node metastasis. Curative resection was intended for the remaining 39 patients; D2 was performed in 27 and D3 in 12. Thus, D2 or D3 was performed in 39 of all eligible 49 patients. Consequently, R0 resection was performed in 38 patients, R1 in 1 due to positive peritoneal cytology, and R2 in 7 due to peritoneal dissemination or extended lymph node metastases (Table 3). Thus, the proportion of R0 resections was 78% (38 of all eligible 49 patients), with a 95 per cent confidence interval from 66% to 89%.

Surgical morbidity and mortality

Surgical complications are shown in Table 4. There was no operative mortality. On the other hand, operative morbidity was observed in 5 of the 49 patients including pancreatic fistula in 1 and abdominal abscess in 2. No anastomotic leakage was observed and no patients required re-operation for morbidity.

Table 2
Adverse events during chemotherapy in all eligible patients ($n = 49$).

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Leukocytes	48	0	1	0	0
Neutrophils	38	4	5	2	0
Hemoglobin	40	7	2	0	0
Platelets	48	0	1	0	0
Total bilirubin	48	1	0	0	0
GOT	46	2	1	0	0
GPT	47	1	1	0	0
ALP	46	3	0	0	0
BUN	45	0	4	0	0
Urine creatinine	47	1	1	0	0
Urine protein	47	1	1	0	0
Anorexia	33	8	5	3	0
Nausea	37	6	4	2	0
Vomiting	42	3	4	0	0
Diarrhea	45	3	1	0	0
Pigmentation	45	3	1	0	0

Table 3
Surgical findings in all operated patients ($n = 49$).

Type of surgery	
Proximal gastrectomy	1
Distal gastrectomy	18
Total gastrectomy	27
Exploratory laparotomy	3
Dissection ($n = 46$)[a]	
D0	4
D1	3
D2	27
D3	12
Combined resection	
Spleen	13
Pancreas	4
Gall bladder	8
Spleen + pancreas	2
None	22
Operation time (minutes)	
Median, range	232, 25–590
Blood loss (ml)	
Median, range	342, 0–2760

[a] Three missing cases were exploratory laparotomy.

Pathological response

Details of pathological data are shown in Table 5. A total of 18 patients were diagnosed as pathological T1 or T2 disease. The pathological response rate in resected patients, defined by the degeneration/necrosis area $\geq 1/3$, was 39%. On the other hand, nodal status, which was classified by 2nd English Edition of Japanese Classification of Gastric Carcinoma, was evaluated in 39 patients who underwent D2 or D3 gastrectomy. Pathological N0 was observed in 8 patients.

Overall survival

Survival time was estimated in all 49 patients who were eligible. Median follow-up period was 31 months from 27 to 38 months. The overall survival curve is shown in Fig. 1. The three-year survival rate was 43.0% with a 95% confidence interval from 35.6% to 50.3%.

Discussion

This multi-institutional phase II prospective trial demonstrated neither treatment-related death nor severe adverse

Table 4
Surgical complications in all operated patients ($n = 49$).

	Number of patients	%
Anastomotic leakage	0	0
Pancreatic fistula	1	2
Abdominal abscess	2	4
Pneumonia	0	0
Ileus	0	0
Wound infection	1	2
Renal dysfunction	1	2

Table 5
Pathological results.

Depth of tumor invasion ($n = 46$[a])	
T1	3
T2	15
T3	19
T4	9

Nodal status[b] ($n = 39$[c])			
	D2	D3	D2/D3
N0	7	1	8
N1	12	3	15
N2	6	4	10
N3	2[d]	4	6

[a] Three missing cases were exploratory laparotomy.
[b] Nodal status was classified according to 2nd English Edition of Japanese Classification of Gastric Carcinoma.[14]
[c] Ten missing cases included exploratory laparotomy in 3, palliative D0 in 4 and palliative D1 gastrectomy in 3.
[d] Two cases were determined by a few lymph nodes of N3 dissected in addition to D2 dissection.

events by preoperative chemotherapy of S-1 plus cisplatin followed by extended surgery, suggesting that this multimodality treatment was safe and feasible.

Surgical mortality

No operative mortality was observed in the study, although 39 of the 49 patients underwent D2 or D3 surgery after preoperative chemotherapy. In the Japan Clinical Oncology Group (JCOG) 9501 phase III trial that compared D2 and D3 resections, mortality rate was reported to be 0.8% in both arms.[12] Thus, our results suggested that mortality of D2 or D3 was not increased by preoperative chemotherapy with S-1 plus cisplatin. In the retrospective study evaluating the feasibility and safety of preoperative chemotherapy of S-1 plus cisplatin followed by D2 dissection, no operative mortality was reported.[20,21] In the MAGIC phase III trial comparing surgery alone versus pre- and postoperative chemotherapy combined with surgery for resectable gastric cancer, operative mortality was 5.6% in the chemotherapy group

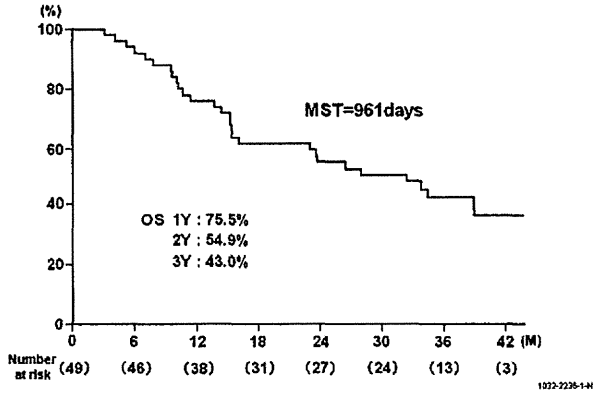

Figure 1. Overall survival ($n = 49$). Median survival time was 31.5 months. Overall survival was 75.5% at 1 year, 54.9% at 2 years, and 43.0% at 3 years.

and 5.9% in the surgery group, suggesting that mortality did not increase by preoperative chemotherapy (with an ECF regimen).[19] However, in that trial, most patients underwent less than D2 surgery. On the other hand, in JCOG 0001 trial evaluating the efficacy and safety of preoperative chemotherapy of CPT-11 plus cisplatin followed by D3 surgery, operative mortality was observed in 2.0%.[13] Thus, operative mortality may depend on the toxicity of the preoperative chemotherapy and the extent of the lymph node dissection.

Pancreas-related surgical morbidity

Pancreatic fistula is the major specific complication after D2 or greater extended surgery. In this study, pancreatic fistula was observed in 1 patient and abdominal abscess in 2 patients. As no apparent anastomotic leak was found in the latter 2 patients, the abdominal abscess might have been caused by pancreatic fistula. Thus, pancreatic fistula might have been a complication in a maximum of 3 of 49 patients in the present study, a proportion almost equivalent to that found in the JCOG 9501 phase III trial.[12] In that trial, tumors were diagnosed as T2–T4, N0–N2, and P0 by surgical findings.[12] In the present study, on the other hand, all tumors were clinically diagnosed as T3–T4. Moreover, 11 of the present patients had clinically apparent N3 disease. Hence, although the tumors were more advanced in this study, the rate of pancreatic fistula was not increased by preoperative chemotherapy with S-1 plus cisplatin. On the other hand, pancreatic fistula was observed in 12.2% in JCOG 0001 trial consisting of CPT-11 plus cisplatin followed by D3 dissection.[13] Toxic regimen could increase the rate of pancreatic fistula.

Overall surgical morbidity

In the present study, overall surgical morbidity was 5 of 49 which was slightly lower than the 20.9% to 28.1% observed in the JCOG 9501 trial.[12] In particular, anastomotic leakage and re-operation were not observed in this study, while rates of these events were 1.9% and 2.7%, respectively, in the JCOG 9501 study.[12] Thus, operative morbidity did not increase with the present preoperative chemotherapy regimen. In the MAGIC trial, morbidity was similar in both arms of the trial; 45.3% in the surgery alone group and 45.7% in chemotherapy group.[19] Because our preoperative chemotherapy was performed only short term, operative morbidity appears not to increase even after D2 or D3 surgery.

Chemotherapy-related toxicities

Chemotherapy-related toxicities were relatively mild in this study. There were no grade 4 toxicities and only a few grade 3 toxicities including neutropenia, anorexia, and nausea. In the SPIRITS trial,[10] grade 3/4 bone marrow suppression was more frequently observed when compared with the present trial. Chemotherapy was limited to one course in this study while it continued until disease

progression in the SPIRITS trial, which would explain the difference in the toxic profile between the two studies. Our results may also suggest that mild toxicities led to high compliance with this chemotherapy regimen and low morbidity and mortality of D2 or D3 resection.

Response to the chemotherapy

The present study achieved a relatively high response rate of 38%, which was almost the same as observed in the pathological response of the primary tumor. Previous trials in metastatic gastric cancer have demonstrated that response rate was 76% in a phase II trial[9] and 54% in the SPIRITS phase III trial.[10] The response rate in this study was slightly lower, which may be attributable to only one course of chemotherapy being administered in the present study. In the MAGIC phase III trial, three courses of ECF chemotherapy were performed preoperatively.[19] Considering the low toxicities of one course of S-1 plus cisplatin and the low mortality and morbidity of subsequent extended surgery, an additional two or three courses of this chemotherapy should be evaluated in another phase II study.

Survival

In the present study, all patients were clinically diagnosed with T3 or T4 disease before entry and overall 3-year survival rate was 43.0%. It has been reported that clinical diagnosis of T3–T4 was accurate in 74.4% in clinical T3 tumors and 87.0% in clinical T4 tumors.[5] M0 was evaluated by computed tomography and diagnostic laparoscopy was not mandatory in this study, therefore, peritoneal metastases may not be excluded in this series.[22] Retrospective analyses of Cancer Institute Hospital of Japan have reported 5-year survival rates of 25.3% and 1.8% in pathological T3 and T4 with any N, respectively.[5] In this series of patients, the 3-year survival rate was 43% despite that R0 resection was only performed in 77.6%. Although it may be difficult to compare these survival rates, our results appear to be worthy of further investigation using the same strategy.

Conclusion

In conclusion, preoperative chemotherapy with one course of S-1 plus cisplatin followed by gastrectomy with D2 or D3 dissection seems to be feasible and safe for clinically serosa-positive (T3–4) gastric cancer.

Acknowledgment

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Conflict of interest

No authors have any conflict of interest.

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The utility of pre-operative peritoneal lavage examination in serosa-invading gastric cancer patients

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Background. *Peritoneal dissemination is frequently found during laparotomy in patients with serosa-invading gastric cancer. Detection of exfoliated cancer cells in abdominal lavage cytology is indicative of stage IV because of its strong association with peritoneal dissemination. Herein we have described peritoneal lavage cytology using a bedside procedure under local anesthesia.*
Methods. *A prospective study of 113 patients with serosa-invading gastric cancer but without peritoneal metastases was performed. A drainage tube was inserted into the abdominal cavity for peritoneal lavage. Patients with negative cytology (CY0) were scheduled for curative gastrectomy.*
Results. *The bedside procedure was performed safely without any complications. Lavage cytology identified CY1 in 35 (31.0%) patients and CY0 in 78 (69.0%) patients. Patients with CY0 underwent laparotomy and peritoneal lavage cytology, and 9 were found to have peritoneal disease (3 with operative CY1, 4 with peritoneal dissemination, and 2 with both operative CY1 and peritoneal dissemination). Two other patients had small, distant metastases. Finally, curative gastrectomy was achieved in 67 (59.3%) patients, but not in 46 (40.7%) patients. Thus, our bedside, pre-operative peritoneal lavage detected 76.1% (35/46) of noncurative disease before operative with a false-negative rate for detecting peritoneal disease of 20.5% (9/44). Patients with pre-operative CY1 had a poorer prognosis than pre-operative CY0 (2-year cause-specific survival 26.6% vs 82.6%).*
Conclusion. *Pre-operative bedside peritoneal lavage under local anesthesia followed by cytology is a simple and safe method for the pre-operative diagnosis of peritoneal dissemination and may help to reduce unexpected, noncurative surgery. (Surgery 2010;148:96-102.)*

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DESPITE RECENT IMPROVEMENTS IN OPERATIVE TREATMENTS, PATIENTS WITH SEROSA-INVADING GASTRIC CANCER show poor a prognosis, with a 5-year survival rate of 25–31%, even after curative resection.[1-4] In particular, peritoneal recurrence is the most frequent recurrence pattern in these patients,[5] with an estimated recurrence rate of 30–50%.[2,6-9] Cytologic examination of peritoneal lavage fluid is a useful predictor of peritoneal dissemination or recurrence, as documented in several studies reporting a close relationship between peritoneal dissemination and free cancer cells in the lavage fluid.[10-14] Furthermore, cases with positive cytology have been reported to show almost comparable poor prognosis to those with peritoneal dissemination.[6,13,15] For this reason, lavage cytology of the abdominal cavity is routinely performed at gastrectomy[6,16] and has been in fact incorporated in the Japanese staging system for gastric cancer since 1998.[17] In this system, positive cytology is classified as stage IV irrespective of other cytologic factors. Because the survival benefits of palliative gastrectomy in stage IV disease, including peritoneal dissemination or positive lavage cytology, have not been elucidated,[18-20] there is a great debate on whether patients with stage IV gastric cancer should be treated initially by palliative gastrectomy or undergo systemic chemotherapy. However, more stage IV patients might choose systemic chemotherapy in the future based on the development of new chemotherapeutic agents or selection of better chemotherapeutic cocktails.[21-25]

Recently, staging laparoscopy has been performed to evaluate peritoneal dissemination in

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advanced gastric cancer with suspected peritoneal metastasis.[26-28] The procedure is usually conducted in the operating room under general anesthesia[29] or local anesthesia with conscious sedation, thus involving physical invasion and expensive medical resources. Thus, in practical terms, it is difficult to apply staging laparoscopy as a routine preoperative examination for all patients with gastric cancers. This is especially true in countries where such cancers are the most common malignant tumors, such as in the Far East, where hundreds to thousands of patients are treated every year in high-volume institutions. In fact, most studies of staging laparoscopy for gastric cancers were conducted in small cohort despite the usefulness of this procedure.[27,28,30,31] Therefore, there is a need for a simpler method that can be available for more patients with advanced gastric cancer and at the same time can be used to accurately evaluate peritoneal dissemination status before selection of further treatment.

Based on this background, we performed pretreatment peritoneal lavage under local anesthesia at bedside in >100 consecutive patients with gastric cancer with suspected serosal invasion. Although this procedure did not include visual inspection of the abdominal cavity, it allowed evaluation of the majority of cases with peritoneal spread of cancer cells owing to the close relationship between exfoliate cancer cells and peritoneal dissemination. Based on the results of peritoneal lavage analysis, one can elect direct administration of chemotherapeutic agents, using the drainage tube placed at the time of peritoneal lavage. In the present study, we report the simple procedure of tube insertion for peritoneal lavage and its clinical usefulness in detecting stage IV disease among serosa-invading gastric cancers.

PATIENTS AND METHODS

Patients and treatment protocol. Between June 2002 and August 2006, 113 patients were enrolled in this prospective study of pre-operative lavage cytology. The inclusion criteria were (1) histopathologically confirmed gastric adenocarcinoma based on examination of endoscopic gastric biopsies; (2) clinical diagnosis of serosal invasion (cT3 or deeper, according to the Japanese staging system for gastric cancer[17]); (3) absence of noncurative factors, such as hematologic metastasis and obvious peritoneal dissemination, based on preoperative examination; (4) no preceding therapies for gastric cancer; (5) no previous laparotomy with associated dense fibrosis and adhesions, other than appendectomy or cholecystectomy; (6) no active bleeding or stenosis owing to the primary lesion; (7) no esophageal invasion of >2 cm in length; (8) no other primary malignancy; and (9) absence of physical disorders that could interfere with gastrectomy.

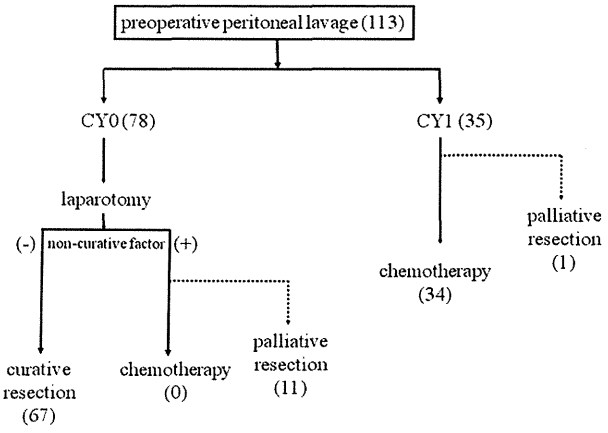

Fig 1. Protocol used for patients with serosa-invading gastric cancer. Chemotherapy, which consisted of a series of intraperitoneal (i.p.) and systemic injections, was used for patients categorized as pre-operative CY1. Patients with pre-operative CY0 received gastrectomy in the absence of other noncurative factors.

The enrolled subjects were 42 women and 71 men with a mean age of 62.5 years (range, 31–79). Details of tumor characteristics were as follows; histological type defined by the Lauren classification[32] (intestinal/diffuse type: 40/73), tumor location (upper/middle/lower: 29/33/51), morphology (type 0/1/2/3/4/5: 12/5/35/36/21/4), cT stage (T3/4:110/3), and cN stage (N0/1: 36/77), both of which are based on the Japanese Classification of Gastric Cancer.[17] The depth of tumor invasion was assessed in all patients by using multidetector row computed tomography (CT) and 3-dimensional imaging,[33-35] which included construction of gastric wall images. Serosal invasion (T3) of gastric tumors was diagnosed when the entire thickened stomach wall was abnormally enhanced and linear or reticular structures were observed in the fatty layer surrounding the stomach. Enrolled patients with positive cytology to chemotherapy and those negative to gastrectomy were assigned to have peritoneal lavage within 1 week after the present examination (Fig 1). Chemotherapy comprised intraperitoneal (i.p.) administration of mitomycin and cisplatin (CDDP), followed by systemic (intravenous) chemotherapy. As postoperative adjuvant chemotherapy for Stage II/III patients with curative resection, we used an S-1 alone regimen, uracil/tegafur (UFT), or 5'-deoxy-5-fluorouridine

(5'-DFUR) regimen. For follow-up, patients were surveyed postoperatively or postchemotherapy every 3 months by physical examination and serum tumor markers, every 6 months by CT scan and abdominal ultrasonography, and every year by endoscopy.

The study protocol was approved by the Human Ethics Review Committee of Osaka University School of Medicine and a signed consent form was obtained from each subject.

Procedure of pre-operative peritoneal lavage and tube insertion. A 14-Fr sump-tube (Argyle) was used as a drainage tube for peritoneal lavage and also as an infusion tube for i.p. chemotherapy. Electrocautery was used for coagulation. A small aseptic cup and 500 mL of saline were used for lavage and collection of the peritoneal cavity lavage fluid for subsequent examination and diagnosis. Local infiltration anesthesia was induced with 1% lidocaine (20 mL) solution.

The patient was placed in supine position without systemic sedation and 1 surgeon performed this procedure with an assistant standing on the other side of the patient. First, a small (2–3 cm) median incision was made 2 cm below the umbilicus after infiltration of the skin and subcutaneous tissue with 1% lidocaine. The wound was bluntly dissected to the fascia using electrocautery and surgical clamps. Then, under additional local anesthesia, the fascia and the muscle fibers were dissected down to the peritoneum. Finally, the peritoneum was lifted up with mosquito clamps and cut with a scalpel to access to abdominal cavity. Then, we inserted a drainage tube into the abdominal cavity together with the surgical probe and placed the tip of the tube into the pelvic cavity behind the urinary bladder and this was confirmed by an abdominal radiograph. The peritoneum and fascia around the tube were sutured and fixed to avoid leakage of peritoneal lavage fluid and infusion solution of i.p. chemotherapy. Next, 500 mL of saline was instilled through the tube. The abdomen was gently shaken to spread the saline fluid throughout the pelvic and abdominal cavities. Then, about 100 mL of peritoneal lavage fluid was drained spontaneously through the tube by changing the patient's position. The lavage specimen was subjected to cytologic analysis if >50 mL of lavage fluid was retrieved. The wound was closed and the tube was fixed to the skin until cytologic diagnosis was reported on the next day.

Chemotherapy protocol. Chemotherapy was provided for patients with positive results on preoperative cytology. The protocol of i.p. chemotherapy consisted of the following: mitomycin at 13 mg/m^2 on day 1 and cisplatin (CDDP) at 13 mg/m^2 on days 1–5 dissolved in 1 L of saline were injected through the drainage tube placed at peritoneal lavage.[36] This was followed by systemic chemotherapy. The protocol was as follows: 1 treatment cycle consisted of continuous intravenous infusion of 5-fluorouracil at a dose of 350 mg/m^2 per day on days 1–5, intravenous drip infusion of cisplatin (CDDP) at a dose of 10 mg/m^2 per day on days 1–5, and drip infusion of docetaxel at a dose of 60 mg/m^2 on day 1. Treatment was repeated twice with an interval of 2–3 weeks. On the other hand, the regimen used for patients with noncurative factors diagnosed at laparotomy was S-1–based chemotherapy.

Cytologic examination of peritoneal lavage fluid. Experienced technologists and cytopathologists examined the peritoneal lavage fluid. After centrifugation of the specimen for 5 minutes at 1,500 rpm, the nucleated cell layer was smeared onto a glass slide and stained by the Papanicolaou technique. The patient was considered to have positive cytology if adenocarcinoma cells were detected, regardless of their number.

Statistical analysis. The correlations between peritoneal cytology status and various clinicopathologic parameters were evaluated by using the Chi-square test and Fischer's exact probability test. Prognostic variables were assessed by the log-lank test, and cause-specific survival was analyzed by the Kaplan–Meier method. In this study, survival time was defined as time from the day of diagnosis to the day of death. These analyses were carried out using The Statistical Package for Social Sciences for Windows release 10 (SPSS Inc., Chicago, IL). $P < .05$ was accepted as significant.

RESULTS

Diagnosis of dissemination using peritoneal lavage fluid. All procedures were safely performed without any serious complications. The mean time required to perform the procedure was about 25 minutes. In all patients, the drainage tube was successfully inserted into the abdominal cavity to retrieve the peritoneal lavage fluid. Cytologic examination was available for all patients tested. Wound pain caused by the procedure was minimal and was controlled in all patients with oral analgesics. After the procedure, mild wound infection occurred in 1 patient, but it was easily controlled after resuturing of the skin.

Thirty-five (31%) patients were diagnosed preoperatively with positive cytology (CY1), classified as stage IV according to the Japanese Classification of Gastric Cancer[17]; the remaining 78 patients

Table. Correlation between peritoneal cytology and clinicopathologic parameters

Parameters	*Cytology*			P *value*
	Positive	*Negative*	*Total*	
Age (yrs)				
<65	16	41	57	.5459
≥65	19	37	56	
Gender				
Male	22	49	71	>.9999
Female	13	29	42	
Histologic type*				
Intestinal	5	35	40	.0015
Diffuse	30	43	73	
Location				
Upper	11	18	29	.3603
Middle, lower	24	60	84	
Morphology				
Type 4	20	68	88	.0010
Others	15	10	25	
cT†				
T3	35	75	110	.5511
T4	0	3	3	
cN†				
N0	7	29	36	.0831
N1	28	49	77	
Total	35	78	113	

*Lauren classification.
†cT, cN, based on the Japanese Classification of Gastric Cancer.

(69%) were classified as cytology negative (CY0). Peritoneal cytology did not correlate with various clinicopathologic parameters such as age, gender, tumor location, or clinical T and N stages, although it correlated with histopathologic type (Lauren classification[32]) and morphology (P = .0015 and .0010, respectively; Table). According to the treatment protocol shown in Figure 1, all preoperative CY0 patients underwent laparotomy and another peritoneal lavage cytology, and 9 (11.5%) patients were then found to have peritoneal dissemination, including 3 patients with operative CY1, 4 with peritoneal dissemination, and 2 with both operative CY1 and peritoneal dissemination. Therefore, the false-negative rate for the bedside peritoneal lavage cytology for detecting peritoneal dissemination was 20.5% (9/44). Excluding these 9 patients and the other 2 patients with small, distant metastases incidentally diagnosed at laparotomy (1 in liver and another in colon), curative gastrectomy was achieved in 67 of 78 (85.9%) pre-operative CY0 patients. On the other hand, 34 out of 35 (97%) patients with pre-operative CY1 received chemotherapy, excluding 1 patient who showed massive bleeding from the primary tumor after enrolment in the study. Palliative gastrectomy was performed in 12 patients; 11 pre-operative CY0 patients with noncurative factors diagnosed at laparotomy and 1 pre-operative CY1 patient with massive bleeding.

The following additional treatments were provided after the described protocol. After curative resection, 28 out of 67 patients received adjuvant chemotherapy (S-1 alone regimen in 25 patients and UFT or 5'-DFUR in 3 patients). All 12 patients who underwent palliative gastrectomy received S-1–based systemic chemotherapy after resection. Among 34 patients with pre-operative CY1 who received chemotherapy, 24 patients underwent either curative or palliative gastrectomy and 10 patients were treated by chemotherapy alone. Lavage cytology was performed again in 26 patients with any response to the chemotherapy. Among them, 17 patients turned to be negative cytology (14 out of 17 patients underwent curative gastrectomy), whereas 9 showed persistent positive cytology after chemotherapy.

Survival analysis. The median follow-up period was 28.8 months. The mean survival time for all 113 patients was 23.9 months. Prognosis of patients initially diagnosed as CY1 (n = 35) was very poor, with a mean survival time of 18.2 months and a 2-year survival rate of 26.6%, compared with 31.0 months and 82.6%, respectively, for patients with CY0 (n = 78; P < .0001; Fig 2, *A*). The 2-year survival rate of patients with curative resection (n = 67) was 90.0%, whereas the corresponding values for palliative resection (n = 12) and chemotherapy (n = 34) were 16.7% and 28.1%, respectively, although the difference was not significant (P = .6981; Fig 2, *B*).

DISCUSSION

The abdominal cavity can be explored by either laparotomy or laparoscopy. In the present study, we attempted an entirely new procedure of bedside tube insertion for peritoneal lavage under local anesthesia. Using this procedure, the frequency of positive cytology (CY1) in serosa-invading gastric cancer was 31.0% (35/113), which was almost similar or somewhat higher than that reported in previous studies by lavage cytology at laparotomy, showing 10–30% of CY1 for patients at the same stage.[6,13,16,37-39] The overall accuracy of detection of peritoneal disease was 92% (104/113), although a few peritoneal diseases were unexpectedly found at laparotomy. Finally, 76.1% (35/46) of patients with noncurative disease could be diagnosed without unnecessary laparotomy based on the present bedside procedure.

Our bedside procedure of tube insertion was designed as a substitution for laparoscopic

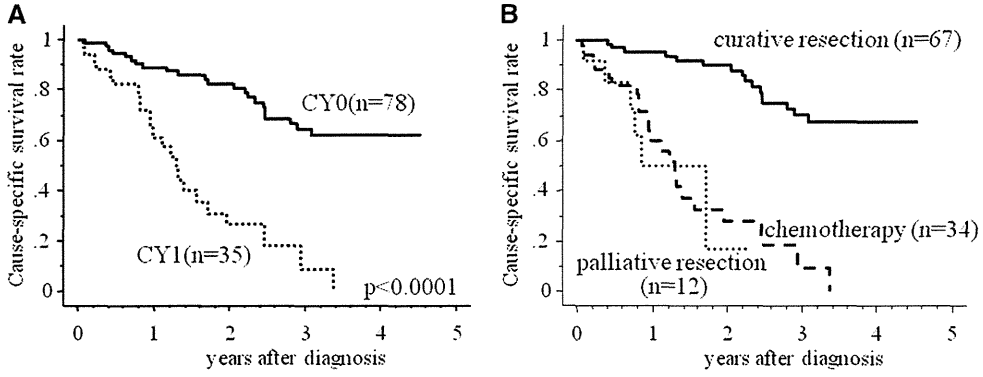

Fig 2. Cause-specific survival curve according to preoperative peritoneal lavage diagnosis and treatment modality. Cause-specific survival curves were plotted by the Kaplan–Meier method. (*A*) Survival curves based on pre-operative peritoneal lavage diagnosis. Differences between the 2 groups were evaluated by log rank test. Ordinate: cause-specific survival rate, Abscissa: time (years) after diagnosis. (*B*) Survival curves based on treatment modality (curative resection, palliative resection, and chemotherapy).

exploration. Because laparoscopic exploration includes lavage cytology and visual inspection, the lack of visual inspection is theoretically the most considerable drawback of our procedure. However, we were able to achieve an overall accuracy of 92.0% (104/113) in predicting peritoneal disease, which was equivalent to that of previous reports using laparoscopic staging, showing 89–95%.[28,31,40-44] These data suggest a close relationship between lavage cytology and macroscopic peritoneal metastasis. In fact, only 4 patients showed peritoneal metastasis despite negative cytology in our series. Because peritoneal cancer nests of these patients were few (2–5 nests) and small (<2 mm in diameter), it is doubtful that they could have been detected by laparoscopic examination. Visual inspection in staging laparoscopy is often of limited value, based on our experience before the present study; only a few cases were found to be CY0P1 by staging laparoscopy. Although improvements in radiologic examination, such as multidetector CT scanning, allow detection of small size peritoneal metastases,[45,46] we anticipate that bedside cytologic analysis to be more commonly used in the future than visual investigation for peritoneal dissemination.

With respect to complications associated with laparoscopy conducted under local anesthesia, Sand et al[47] reported that 5 (2%) of 215 patients developed complications; including small bowel perforation (n = 1), bleeding from the abdominal wall (n = 1), atrial fibrillation (n = 1), and wound infection (n = 2). Nagahama et al[48] concluded that laparoscopic examination was easier and more feasible under general than local anesthesia owing to the high abdominal pressure by abdominal pain accompanied by the pneumoperitoneum. On the other hand, our procedure is feasible enough requiring just local anesthesia at the bedside without any monitors based on the negligible frequency of complications (only 1 patient developed wound infection). Moreover, the low cost of our procedure provides a major advantage; the estimated cost is about US$45, which is only about one ninth of the US$399 cost of staging laparotomy under the general anesthesia with intraoperative cytology. Although these estimates include only the expenses of the materials used in the procedure and cytologic examination, the difference in the total costs is expected to be much greater when considering other costs, such as those related to the use of the operating room, personnel, and equipment.

Based on its invasiveness, the risk of complications, and relatively high cost, studies of preoperative laparoscopy have been limited to relatively small cohorts,[27,28,30,31] and some investigators have suggested that laparoscopy should be limited to patients who have radiologic suspicion of peritoneal metastasis on spiral CT.[49] We regard the indication of preoperative abdominal examination to be T3/4 stage, which accounts for about 20–40%[6,50] of gastric cancer patients in Japan. On the other hand, in Western countries, where gastric cancer is less common but diagnosed at more advanced stages, staging laparoscopy has been more commonly performed. Our bedside procedure would be beneficial for patients and helpful in saving medical resources in these countries.

Although the primary purpose of this study was to describe the detection of stage IV disease through a simple and easy-to-perform bedside procedure, treatment of stage IV gastric cancers is another issue to be discussed here. There is

controversy regarding the role of palliative gastrectomy and whether or not it should be substituted by chemotherapy in such patients. Over many decades, surgery had been the only reliable treatment for gastric cancers; however, palliative gastrectomy confers little survival benefits for patients with stage IV disease,[18-20] with the added risks of operative morbidity, mortality, prolonged hospitalization, and potentially inferior quality of life.[19,51-54] On the other hand, recent advances in chemotherapy for inoperable gastric cancers[21-25] may allow this therapeutic modality to become the choice of treatment instead of operation in the near future. In the present series, we used chemotherapy for pre-operative CY1 patients and palliative gastrectomy for pre-operative CY0 patients who incidentally were found to have non-curative factors at laparotomy. There were several reasons for the use of palliative gastrectomy as clinical practice for the latter. In this study, pre-operative CY1 patients underwent both systemic and peritoneal chemotherapy. Peritoneal chemotherapy might be difficult after laparotomy because of adhesions in the abdominal cavity. Another point is that palliative gastrectomy may still be beneficial when residual disease is very small. However, it is noteworthy that there was no survival difference between palliative gastrectomy and chemotherapy (Fig 2, *B*), despite the former, which was mostly pre-operative CY0, should mean less tumor burden in the abdominal cavity than the latter, which was mostly pre-operative CY1. Taken together, treatment of stage IV gastric cancers, that is, palliative gastrectomy or chemotherapy, is an important issue that needs to be investigated in a large cohort study in the future.

Our bedside procedure, similar to staging laparoscopy, allowed us to accurately diagnose peritoneal dissemination pre-operatively in the majority of patients. This is very useful in clinical practice because surgeons and patients have enough time to discuss various treatment options, prognosis, and quality of life. Otherwise, when meeting the unexpected peritoneal disease at laparotomy, surgeons make the decision alone or close the abdominal cavity without discussion. To avoid such a situation, one should try to obtain as much as possible information about the spread of cancer in the abdomen before laparotomy.

In conclusion, our new procedure of pre-operative bedside peritoneal lavage under local anesthesia is simple, safe, and could be regarded as an established method. We successfully detected the majority of stage IV gastric cancers and replaced part of palliative gastrectomy with peritoneal and systemic chemotherapy by using pre-operative lavage cytology.

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