recommended dose in Japan (8, 23, 24). Furthermore, reduced dose 5-FU and split low-dose CDDP have been introduced to reduce the adverse events (28, 29). The aim of this study was to evaluate the toxicity and efficacy of a docetaxel, low-dose 5FU and split low-dose CDDP combination for AGC as an induction chemotherapy.

Patients and Methods

Patients. Patients with locally advanced and/or distant metastatic gastric cancer who were treated at Osaka University Hospital (Osaka, Japan) between October 2001 and January 2008 were enrolled in this study. Staging laparoscopy was performed for patients with serosa-invading gastric cancer to detect peritoneal dissemination. The inclusion criteria were as follow: age, 20-75 years; no prior chemotherapy; ECOG performance status, 1 -2 (30); existence of measurable target lesions by RECIST criteria (31); adequate function of major organs; no other active malignancy; estimated life expectancy of more than 3 months and provision of written informed consent. Patients were excluded if they were found to have severe co-morbid conditions, infectious diseases, brain metastasis, massive pleural effusion, massive pericardial effusion, peripheral neuropathy or a past history of drug allergy. Furthermore, pregnant and breast-feeding women were also excluded. The patients were classified according to the Japanese Classification of Gastric Cancer (32). The study protocol was approved by the Human Ethics Review Committee of Osaka University School of Medicine.

Treatment regimen. The regimen used for the treatment of the enrolled patients is illustrated in Figure 1. This regimen was repeated every 4 weeks for a total of 2 cycles. All the patients underwent hematological tests and physical examination before the start of each course. If the following toxicities occurred, the next administration was delayed until full recovery from the toxicity and the doses of all the drugs (docetaxel, 5-FU, and CDDP) were reduced by 25% in the following course: leukocyte count <3000/μl; platelet count $<10.0\times10^4$/μl or non-hematological toxicity of ≥grade 3. If complete resection was expected or the non-curative resection factor was liver metastasis only, surgery was attempted 2-4 weeks after the chemotherapeutic regimen. The primary end point was the overall response rate for chemotherapy, while the secondary end points were OS, the toxicity profile and the rate of complete resection.

Evaluation of toxicity, response and survival. Blood cell counts and blood chemistry (including liver and renal function tests) were performed at least once a week. The toxicity of the chemotherapy was monitored and graded according to the Common Toxicity Criteria of the National Cancer Institute version 2.0 (http://www.cancer.gov). The tumor response was assessed by computed tomography at every cycle of treatment and evaluated by the Response Evaluation Criteria in Solid Tumor (RECIST) (31). The RECIST criteria are defined as follows: complete response (CR), the disappearance of all target lesions; partial response (PR), at least a 30% decrease in the sum of the longest diameters of the target lesions, taking as reference the baseline sum of the longest diameters; progressive disease (PD), at least a 20% increase in the sum of the longest diameters of the target lesions, taking as reference the smallest sum of the longest diameter recorded since the treatment started or the appearance of one or more new lesions; stable disease (SD), neither sufficient shrinkage to quality for PR nor sufficient increase to quality for PD, taking as reference the smallest sum of the longest diameter since the treatment started.

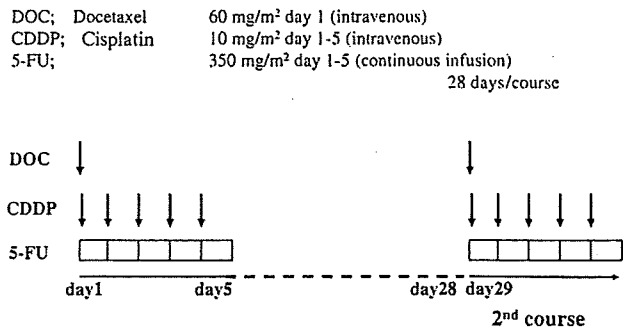


Figure 1. *Treatment regimen. The regimen was repeated every 4 weeks for a total of 2 cycles.*

Statistical analysis. Numerical values are expressed as the median (range). Survival was defined from the first day of chemotherapy to death from any cause and calculated by the Kaplan-Meier method. All the calculations were performed with the software package Statview Version 5.0 (SAS Institute, Inc, Cary, NC, USA).

Results

Patient characteristics. A total of 18 patients with AGC (adenocarcinoma) were enrolled in this trial. The Eastern Cooperative Oncology Group performance status was 0 or 1 in 16 (89%) patients. The reasons for induction chemotherapy were bulky N2 lymph node (LN) metastasis in 3 patients, N3 metastasis in 5 patients, tumor invasion of adjacent organs (T4) in 3 patients, liver metastasis in 3 patients, lung metastasis in 2 patients, distant LN metastasis in 1 patient and peritoneal dissemination in 1 patient. The patient characteristics are listed in Table I.

Adverse events. Eighteen patients received a total of 32 treatment cycles. The average number of cycles administered per patient was 1.8. Four patients received only one cycle of chemotherapy, two were due to tumor progression and two due to toxicity and deterioration of performance status. The most common adverse events were gastrointestinal toxicity, leukocytopenia and neutropenia. Grade 3 anorexia and nausea occurred in 16.7% and 11.1% of the patients, respectively. Grade 4 leukocytopenia and neutropenia occurred in 5.6% and 27.8%, respectively. The adverse events are summarized in Table II.

Response to induction chemotherapy. None of the 18 enrolled patients showed a CR, while 8 showed PR, 8 showed SD, and 2 showed PD by the RECIST criteria. The overall response rate was 44.4%. The response rate in the intestinal type primary tumors was 33.3% and in the diffuse type was

Table I. *Patient characteristics.*

n		18	
Median age (range)		57 (35-75)	
Male/Female		15/3	
ECOG-PS 0/1/2		4/12/2	
Borrman type 1/2/3/4		1/6/8/3	
Histopathological type			
Intestinal/diffuse6/12			
Localization U/M/L		6/5/7	
cStage IIIB/IV		3/15	
Non-curative resectable factor			
Bulky N2	3	N3	5
T4	3	H1	3
Lung	2	P1	1
Distant LN	1		
Mean no. of treatments (range)		1.8 (1-2)	

ECOG: Eastern Cooperative Oncology Group, PS: performance status, LN/N: lymph node, U: upper third portion of the stomach, M: middle third portion of the stomach, L: lower third portion of the stomach, T4: tumor invasion of adjacent structures, H1: liver metastasis, P1: peritoneal dissemination.

50.0%. The response rate for each target organ is listed in Table III. Histopathological examination showed no residual tumors (grade 3) in resected specimens of one patient.

Surgery. Gastrectomy was conducted in 15 out of the 18 patients. Surgery was considered curative in 11 patients and non-curative in 4 patients. The two patients with lung metastasis and one patient with distant lymph node metastasis were excluded. Total gastrectomy was performed in 8 patients, distal gastrectomy in 6 patients, and pancreato-duodenectomy in one patient due to tumor spread to the pancreatic head. Extended surgery was conducted in 10 patients: para-aortic lymphadenectomy in 6 patients, partial hepatectomy in 2 patients, left pancreatectomy and splenectomy in 1 patient and transverse colectomy in 1 patient. The Roux-en Y reconstruction technique was performed after gastrectomy in all the patients who underwent gastrectomy. The median operative time was 295 min and the median blood loss during surgery was 970 ml. The median duration of hospital stay after surgery was 21 days. Postoperative complications developed in 6 patients and the overall morbidity rate was 40%. Pancreatic fistula developed in 2 patients, liver infarction in 1 patient, liver dysfunction in 1 patient, abdominal abscess in 1 patient, bowel obstruction in 1 patient and peritoneal paralysis in 1 patient.

A repeat operation was performed in 1 patient with suspected liver infarction, and cholecystectomy and reconstruction of the hepatic artery were performed for the patient. One patient (6.7%) died of liver failure three months after surgery due to progressive disease of hepatitis C liver cirrhosis. Out of the 11 patients who underwent curative-surgery, 8 received adjuvant chemotherapy (oral S-1 after surgery).

Table II. *Adverse events (n=18).*

	Grade 1 No. (%)	Grade 2 No. (%)	Grade 3 No. (%)	Grade 4 No. (%)
Non hematological toxicity				
Alopecia	3 (16.7)	3 (16.7)	0 (0)	0 (0)
Fatigue	5 (27.8)	3 (16.7)	0 (0)	0 (0)
Anorexia	2 (11.1)	1 (5.6)	3 (16.7)	0 (0)
Nausea	7 (38.9)	2 (11.1)	2 (11.1)	0 (0)
Stomatitis	3 (16.7)	0 (0)	0 (0)	0 (0)
Hematological toxicity				
Leukocytopenia	0 (0)	8 (44.4)	6 (33.3)	1 (5.6)
Neutropenia	1 (5.6)	4 (22.2)	6 (33.3)	5 (27.8)
Anemia	1 (5.6)	5 (27.8)	2 (11.1)	0 (0)
ALT	2 (11.1)	0 (0)	0 (0)	0 (0)

National Cancer Institute Common Toxicity Criteria Version 2.0; ALT: alanine aminotransferase.

Table III. *Tumor response to chemotherapy (n=18).*

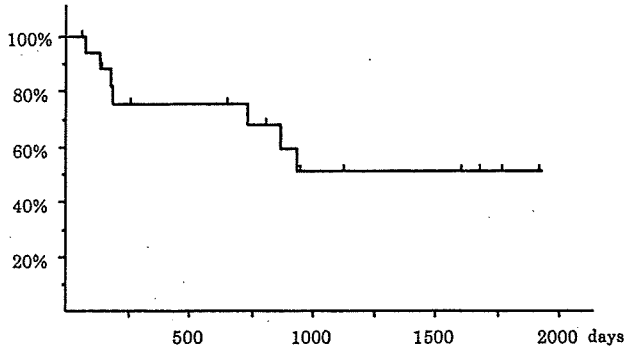
	No (%)				
	CR	PR	SD	PD	RR
Overall	0 (0)	8 (44.4)	8 (44.4)	2 (11.1)	44.4%
Metastases					
LN (17)	0 (0)	8 (47.1)	9 (52.9)	0 (0)	47.1%
Liver (3)	0 (0)	2 (66.7)	0 (0)	1 (33.3)	66.7%
Lung (2)	0 (0)	0 (0)	2 (100)	0 (0)	0%
Peritoneal (1)	0 (0)	0 (0)	1 (100)	0 (0)	0%
Histological type					
Intestinal (6)	0 (0)	2 (33.3)	3 (50.0)	1 (16.7)	33.3%
Diffuse (12)	0 (0)	6 (50.0)	5 (41.7)	1 (8.3)	50.0%

Evaluated by RECIST, CR: complete response, PR: partial responses, SD: stable disease, PD: progressive disease, RR: response rate, LN: lymph node metastasis.

Survival. The median survival had not been reached after a median follow-up of 40 months. The 1- and 3-year survival rates were 75.6% and 51.1%, respectively. Figure 2 depicts the survival curve of all 18 patients calculated by the Kaplan-Meier method.

Discussion

The phase III V325 trial showed that DCF therapy had significant benefits for OS, time to progression and response rate compared to the CF therapy but as mentioned, grade 3 to 4 toxicity occurred in many of the patients (82%). In a Swiss randomized phase II trial, the trio therapy was modified as docetaxel 75 mg/m^2, CDDP 75 mg/m^2 on day 1 plus 5-FU divided into 1-14 days



Median observation period	1-year survival rate	3-year survival rate	MST
1,256 days (72-2,342)	75.6%	51.1%	1,932 days

Figure 2. *Overall survival curve calculated by the Kaplan-Meier method for all 18 patients enrolled in this study.*

infusion of 300 mg/m^2 (33). Grade 3 or 4 neutropenia occurred in 80% and febrile neutropenia in 41% of the patients compared to 29% in the V325 trial. According to these results, we considered that the triumvirate therapy should be modified to a reduced dosage form especially for induction chemotherapy before surgery. Two late phase II trials performed in Japan recommended that docetaxel should be administered intravenously at a dose of 60 mg/m^2 every 3-4 weeks (23, 24). Therefore, the dose of docetaxel was reduced to 60 mg/m^2 and low-dose continuous 5-FU and CDDP was selected. With these modifications, the incidence of grade 3/4 neutropenia and non-hematological toxicity decreased to 61.1% and 27.8%, respectively. Furthermore, febrile neutropenia was only noted in 5.6% of the patients. The adverse events in the present study were acceptable and no treatment-related death was observed. However, one patient with hepatitis C-related liver cirrhosis died three months after surgery. The patient initially recovered after surgery, but the disease status of liver failure progressed after that, suggesting a possible association with the induction chemotherapy. The less toxic regimen showed an overall response rate (PR and CR) by RECIST of 44.4% in the 18 patients. The lymph node and liver metastases showed higher responses 47.1% and 66.7% of the affected patients respectively, but the lung metastases in the two affected patients showed no response. The response rate was in concordance with the reported rate of 36.6% in the Swiss trial (33) and 37% in the V325 study (27).

In conclusion, along with excellent efficacy and moderate toxicity, the reduced dose combination chemotherapy of docetaxel, 5-FU and CDDP is feasible as an induction chemotherapy for patients with AGC.

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同時性肝転移を伴う胃癌症例に対して肝動注化学療法と手術療法の併用による長期生存例

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A Long-Term Survival Case of Gastric Cancer with Liver Metastases Treated by Hepatic Arterial Infusion Chemotherapy: Toru Masuzawa, Yoshiyuki Fujiwara, Shuji Takiguchi, Makoto Yamazaki, Hiroshi Miyata, Kiyokazu Nakajima, Toshiro Nishida, Masaki Mori and Yuichiro Doki (*Dept. of Gastroenterological Surgery, Graduate School of Medicine, Osaka University*)

Summary

Although systemic chemotherapy has been recognized as a standard treatment for gastric cancer with synchronous hepatic metastasis, the survival benefit of the therapy is still unsatisfactory. On the other hand, the local effect of intra-hepatic arterial chemotherapy (HAIC) is very high, and HAIC combined with systemic chemotherapy and surgery will be an effective therapy for selected patients. Here, we report a 39-year-old female case with advanced gastric cancer and synchronous liver metastasis. She has been treated with systemic chemotherapy, HAIC, and two operations. She has survived for 33 months now. The HAIC therapy will be a promising therapy in combination with systemic chemotherapy and/or surgery for gastric cancer with synchoromous liver metastasis. Key words: Gastric cancer, Liver metastasis, Intra-hepatic arterial chemotherapy

要旨　胃癌の同時性肝転移に対して全身化学療法が標準的な治療の一つであるが，その成績は決して良好とはいえない。一方で，当院で実施した胃癌の肝転移に対する肝動注化学療法が良好な成績を示したため，同時性肝転移症例の長期生存例について1例を報告する。症例は39歳の女性。多発肝転移を伴った進行胃癌を認めた。5-FU/CDDP/DOCの併用療法を2サイクル実施後，胃，肝以外の臓器に新たな病変を認めず，肝病変が縮小傾向を示したため幽門側胃切除術を実施した。術後に全身化学療法を再開したが，肝病変の増悪を示したため肝動注化学療法を実施した。以後約2年間，病変が縮小を示した状態で経過したため肝部分切除術を実施し，現在まで生存中である。本症例は初回治療開始後33か月経過した長期生存例であり，切除不能な胃癌同時性多発肝転移に対して胃切除術と肝動注化学療法の併用が有効な治療法の一つになり得ることが示唆された。

はじめに

胃癌の同時性肝転移症例に対しては，全身化学療法が標準的治療であると考えられるが，その成績は当院の集計でも約1年と決して良好とはいえない。一方で，当院では転移性肝癌に対して積極的に肝動注化学療法を実施しており，その局所コントロール率は高い。今回われわれは，胃癌同時性肝転移に対して全身化学療法＋外科的切除＋肝動注化学療法の併用を施行し，長期生存する症例を経験したので報告する。

I. 当院での肝動注化学療法の成績

2000年9月から2007年1月までに胃癌の肝転移16症例（同時性3例，異時性13例）に対して肝動注化学療法を実施した（表1）。いずれも手術後あるいは再発後に，5-FU (500 mg/day を5日間連続投与)，adriamycin (35 mg/body を day 1 に投与)，cisplatin (CDDP 10 mg/body を day 1 に投与) の3剤併用療法（FAP肝動注化学療法）を3週間で1サイクルとして実施した。16例でのFAP肝動注化学療法の平均施行回数は9.3回，効果判定はCR 4例，PR 9例であり，response rateが81.3%で動注開始後平均生存日数が26.6か月であった。

II. 症　例

患者: 39歳，女性。

主訴: 上腹部痛。

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表 1 当院にて肝動注化学療法を実施した同時性あるいは異時性の胃癌肝転移症例16例

症例	年齢/性別	癌腫	Type	肝転移	肝動注施行回数	効果判定	動注後生存日数(か月)	転帰
1	39/F	MK	同時性	Multiple	21	PR	26.4	生存
2	72/M	MK	同時性	Multiple	7	PR	15.8	生存
3	59/M	MK	同時性	Multiple	8	CR	56.1	生存
4	65/M	MK	異時性	Multiple	4	PR	53.6	原病死
5	74/M	MK	異時性	Multiple	6	CR	36.9	原病死
6	52/M	MK	異時性	Multiple	8	PR	15.3	原病死
7	69/M	MK	異時性	Multiple	14	PR	34.7	原病死
8	73/M	MK	異時性	Multiple	14	CR	34.1	原病死
9	66/M	MK	異時性	Multiple	15	PR	14.9	原病死
10	74/M	MK	異時性	Single	6	PR	5.7	原病死
11	61/M	MK	異時性	Multiple	8	CR	60.3	原病死
12	55/M	MK	異時性	Multiple	14	PR	17.2	原病死
13	66/M	MK	異時性	Multiple	9	NC	7.4	原病死
14	48/M	MK	異時性	Single	5	NC	23.1	原病死
15	77/M	MK	異時性	Multiple	5	NC	7.5	原病死
16	72/M	MK	異時性	Multiple	9	PR	16.3	原病死

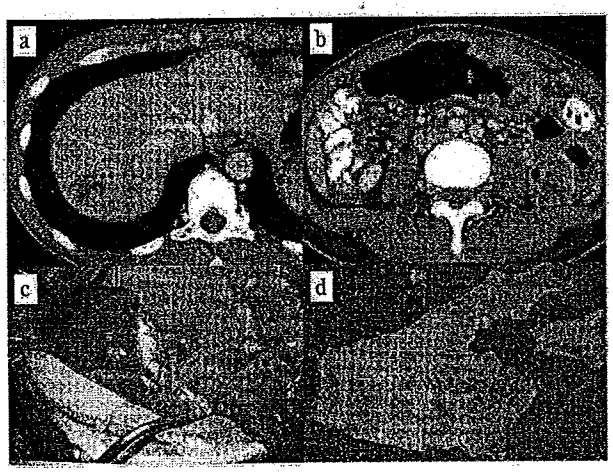

図 1 初回診察時造影CT検査と手術時写真
a,b: 造影CT検査。c: 術中写真。d: 切除標本。

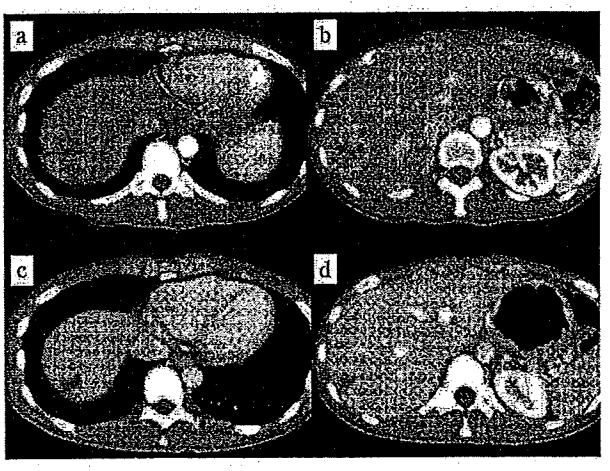

図 2 肝転移病変の造影CT検査
a,b: 術後追加全身化学療法後。c,d: 肝動注化学療法後。

家族歴，既往歴: 特記すべきことなし。

現病歴: 2005年5月より上腹部痛を自覚した。近医受診の上，上部消化管内視鏡検査にて胃癌と診断され，2005年7月当院を受診となる。

上部消化管内視鏡検査: 胃体下部大弯に半周性の2型病変を認めた。

腹部造影CT検査: 胃角部大弯に漿膜外浸潤を伴う主病変と，肝の両葉に多発する転移性病変を認めた(図1a,b)。

内視鏡下生検組織: 低分化腺癌と診断した。

治療経過: 進行度をcT2N1M0H1，cStage IVと診断し，2005年8月より5-FU/CDDP/docetaxel (DOC) の3剤併用療法を2サイクル実施した。この間，肝以外に他臓器転移を認めず，病変も縮小効果を認めたため病変コントロールを目的とした幽門側胃切除術を9月に実施した（図1c,d)。切除標本からの病理学的進行度はpT2N1H1P0，pStage IVと診断された。術後に残存病変に対して最初にS-1単独経口内服，次に5'-DFUR/DOC併用療法を行ったが，肝病変が増悪したため（図2a,b)，2006年2月より肝動注化学療法としてFAP療法を実施した。以後病変は縮小傾向を示し，約1年間コントロールできた（図2c,d)。2007年5月にポート閉塞を認め，同時にPHA狭窄も認めたことから動注カテーテルの再留置が不可能と判断し，肝病変の栄養血管となっている右横隔膜動脈よりTAIを三度実施した。1年経過後も肝以外に病変を認めず，肝病変もS7に限局されたため，2008年4月に肝S7部分切除術を実施した。現在で肝転移診断後約33か月経過したが，残存病変もなく生存中である。

III. 考　察

胃癌の同時性肝転移は進行度がStage IV期であり，特に多発転移の場合，切除不能胃癌と考えられる。切除不能進行・再発胃癌の予後は過去の報告でも1年未満とされており[1,2]，S-1/CDDP併用療法の報告でMSTが約12か月である[3]。このため，われわれは局所コントロールに優れた肝動注化学療法を併用し，平均生存日数が約41.8か月（同時性肝転移3例の平均）と良好な成績を示した。しかし，肝転移が存在している時点ですでに全身に転移している可能性があることを考慮すれば，動注療法を実施する症例は限定されなければならない。当院としては，①全身化学療法が効果を認め，②肝以外に非治癒因子が存在しないことが条件と考えている。症例数が少なく，対照が限定されることより断定的なことはいえないが，ある特定の病態群においては胃切除と肝動注化学療法を含めた集学的治療を行うことで，長期生存を期待させる症例であった。

結　語

肝転移を伴う胃癌症例において，胃切除と肝動注化学療法の併用療法は有効な治療法の一つであることが示唆された。

本論文の要旨は第30回日本癌局所療法研究会において発表した。

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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;■:■-■.)*

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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.

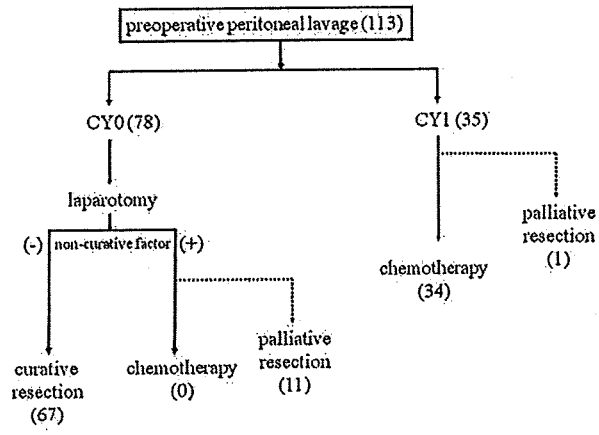

Fig 1. Protocol used for patients with serosa-invading gastric cancer. Chemotherapy, which consisted of a series of intraperitoneal (i.p.) and systemic injections, was used for patients categorized as pre-operative CY1. Patients with pre-operative CY0 received gastrectomy in the absence of other noncurative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

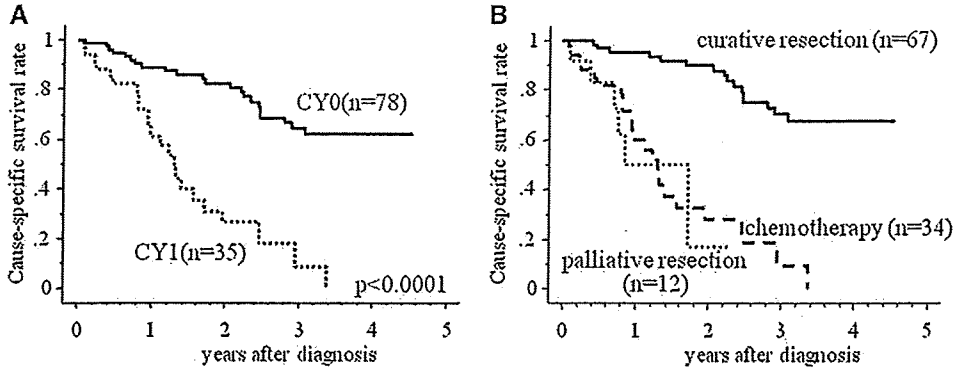

Fig 2. Cause-specific survival curve according to preoperative peritoneal lavage diagnosis and treatment modality. Cause-specific survival curves were plotted by the Kaplan–Meier method. (*A*) Survival curves based on pre-operative peritoneal lavage diagnosis. Differences between the 2 groups were evaluated 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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