## Adjuvant treatment, in conjunction with gastrectomy, for advanced gastric cancer

Surgery has been a central treatment of gastric cancer, though the extent of lymph node dissection has been a controversial subject between the West and the East. Control of local failure is an important issue in the West because of the high local relapse rate. While D1 or D0 has been common in the West, D2 has been standard in Japan, and the combined resection of invaded organs or radical lymphadenectomy has been employed in advanced disease to increase curability and the local control rate. Randomized studies have been carried out to establish the optimal level of lymph node dissection.[10–12] The percentages of local recurrence in these trials were: 41% in D1 and 29% in D2 in the Dutch trial;[10] 30% in D1 and 19% in D2 (old definition: D3) in the Taiwanese trial;[11] and 24% in D2 and 23% in D3 in the Japan Clinical Oncology Group (JCOG) 9501[12] (Table 1) D2 surgery in the treatment of gastric cancer is indicated to control local recurrence, and this surgery appears to correspond to a "plateau level", because no difference in local recurrence rate (including lymph node and peritoneal recurrence) was observed between D2 and D3 surgery.

Evidence for the benefit of adjuvant treatment in patients with resected gastric cancer has been provided by phase III trials conducted both in the West and Japan (Table 2). It was shown that postoperative CT with fluorouracil (F) + leucovorin (L) followed by CRT (45 Gy with FL) conferred about a 10% survival benefit compared to surgery alone in the INT 0116 trial.[3] Though D2 surgery was required in the protocol, the result showed that the surgery actually performed was D0 (54%) and D1 (36%). The study concluded that when insufficient surgery (D0/1) is carried out, postoperative CRT is mandatory. Adjuvant CRT may provide better local control, but the question needs to be asked if CRT provides a survival benefit after D2 surgery. In Japan, a randomized phase III study[14] was conducted in patients with stage II/III gastric cancer, comparing surgery alone with postoperative CT (S-1, 80 mg/m$^2$ for 1 year). The level of surgery was D2. The results of the study demonstrated that treatment with S-1 conferred a significant survival benefit (3-year overall survival rate of 80.5% in the S-1 arm vs 70.1% in the control arm). Postoperative CT alone seems to be sufficient after D2 surgery. It is interesting to observe the results of the Korean study,[15] in which patients were treated with the same CRT regimen as in the INT 0116 trial after D2 surgery, and a comparison was made with patients who underwent surgery alone during the same period. Patient backgrounds in the Korean study were almost identical to those in the ACTS-GC trial[14] in terms of T and N stages. The 3-year survival of the patients receiving CRT in

**Table 1.** Results of three randomized trials evaluating lymph-node dissection in gastrectomy

| | Dutch trial[10] | Taiwanese trial[11] | JCOG trial[12] |
|---|---|---|---|
| Morbidity | D1, 25%<br>D2, 43% | D1, 7%<br>D2, 17% | D2, 20.9%<br>D3, 28.1% |
| Mortality | D1, 4%<br>D2, 10% | D1, 0%<br>D2, 0% | D2, 0.8%<br>D3, 0.8% |
| 5-Year overall survival | D1, 45%<br>D2, 47% | D1, 54%<br>D2, 60%; SD | D2, 69.2%<br>D3, 70.3% |
| Stage migration | 30% in D2 | 8% in D2 | 9% in D3 |
| LN metastasis | N2 (Number), 12% | N2 (Station), 24% | N3 (Station), 8.8% |
| Percentage of local recurrence[a] | D1, 41%<br>D2, 29% | D1, 30%<br>D2, 19% | D2, 24%[b]<br>D3, 23% |

SD, significant difference
[a] Includes local recurrence and local plus distant metastasis
[b] Lymph-node and peritoneal metastasis

**Table 2.** Results of adjuvant treatments for gastric cancer

| | INT 0116[3] RCT | MAGIC Trial[13] RCT | ACTS-GC[14] RCT | Korea[15] Non-RCT |
|---|---|---|---|---|
| Control arm | Surgery<br>$n$ = 275 | Surgery<br>$n$ = 250 | Surgery<br>$n$ = 530 | Surgery<br>$n$ = 446 |
| Test arm adjuvant therapy | Postoperative FL + RT (45 Gy)<br>$n$ = 281 | Perioperative ECF<br>$n$ = 253 | Postoperative S-1<br>$n$ = 529 | Postoperative FL + RT (45 Gy |
| Survival | Control arm<br>5-Y, 28%<br>Test arm 5-Y, 45% | Control arm<br>5-Y, 25%<br>Test arm 5-Y, 35% | Control arm<br>3-Y, 70%<br>Test arm 3-Y, 81% | Control arm<br>3-Y, 61%; 5-Y, 51%<br>Test arm 3-Y, 66%; 5-Y, 57% |
| Surgery | D0, 54%<br>D1, 36% | D1, 20%<br>D2, 41% | D2 | D2 |
| Treatment compliance | 64% | 40% | 65.8% | 75.2% |
| T3 (C vs T) | 61% vs 62% | 55% vs 44% | 43% vs 44% | 38% vs 44% |
| N(+) (C vs T) | 84% vs 85% | 73% vs 69% | 87% vs 91% | 91% vs 94% |

F, fluorouracil; L, leucovorin; E, epirubicin; C, cisplatin; RT, radiation therapy; RCT, randomized control trial; Y, year

**Table 3.** Ongoing investigations of adjuvant therapy for gastric cancer

| |
|---|
| CT Trials |
| MAGIC-B ($n$ = 1100) |
| Perioperative ECX +/– BV |
| SAKK 43199 ($n$ = 240) |
| Preoperative DCF (four cycles) vs postoperative DCF |
| RT Trials |
| CALGB 80101 ($n$ = 536) |
| ECF + CRT + ECF vs FL + CRT + EL |
| CRITICS ($n$ = 788) |
| Perioperative ECX (three cycles) +/– RT |
| GI Cancer Intergroup (in planning) |
| Preoperative CT (FLC) followed by CRT (F + TXL + 45-Gy RT) vs preoperative CT (TXL/C) followed by postoperative CRT (FL + 45-Gy RT) |

E, epirubicin; L, leucovorin; X, xeloda; BV, bevacizumab; C, cisplatin; D, docetaxel; TXL, paclitaxel; RT, radiation therapy

the Korean study was 66%, whereas that in the ACTS-GC trial was 81%. Adjuvant CRT is not necessary after D2 surgery, so that a randomized study comparing D2 plus adjuvant CRT with D2 plus adjuvant CT would not be warranted in Japan. Another agent (cisplatin, or CPT-11 [irinotecan], or taxanes) in combination with S-1 could be the next candidate for adjuvant CT in stage III gastric cancer. A JCOG feasibility study of S-1 plus cisplatin for three courses followed by S-1 for 1 year after D2 is ongoing and needs to be completed before a future phase III trial can be started.

The benefits of neoadjuvant treatment are that it may control micrometastasis, increase resectability and curability, and have high treatment compliance compared to postoperative treatment. Neoadjuvant CRT designed and conducted in the United States has been reported in various studies.[4–6]

A phase II study[6] (Radiation Therapy Oncology Group [RTOG] 9904) comprising preoperative FLC followed by CRT (45 Gy with F and paclitaxel) showed an R0 resection rate of 77% and pathological complete response (pCR) rate of 26%, and median survival was 23.2 months in 50% of patients who underwent D2 surgery. Though preoperative CRT had a high clinical response, toxicities were substantial; grade 4 toxicities were reported in 21% of patients and 14% had surgical complications higher than grade 3. While neoadjuvant CRT yielded a high pCR rate and good curability of surgery, the benefit of RT in conjunction with CT needs to be confirmed. A European study, the MAGIC trial[13] compared three preoperative courses of epirubicin (E), cisplatin (C), and F (ECF) + three postoperative courses of ECF with surgery alone. The result showed that perioperative ECF conferred a survival benefit when compared with surgery alone. Considering the level of compliance for preoperative and postoperative ECF (86% vs 42%), it appears that chemotherapy has the greatest effect when administered preoperatively, with downstaging of both T and N stages observed. Neoadjuvant treatments may confer a survival benefit in gastric cancer. Neoadjuvant treatment has generated a high level of interest, and there are now many ongoing phase III trials in the West (Table 3). Among them, the CRITICS trial has been designed to compare perioperative EC xeloda (X) with and without RT, which may prove the significance of RT. At present in Japan, candidates for neoadjuvant treatment are patients with a poor prognosis, such as type 4 and large type III tumor (more than 8 cm in size), tumor with N3 or bulky N2 metastasis, or locally advanced tumor, because prognosis after curative resection with adjuvant S-1 is reasonably good even in patients with T3 or node-positive tumors. Although neoadjuvant treatment is time-consuming, it has good compliance. A randomized phase III trial (JCOG 0501) is now ongoing. The aim of this study is to evaluate the survival benefit of S-1 plus cisplatin as neoadjuvant chemotherapy in gastric cancer patients with resectable type 4 (linitis plastica type) and large type III tumor in comparison with surgery plus postoperative S-1. The result of this study could confirm that neoadjuvant CT has a useful role to play in such patients.

## CRT for unresectable/recurrent tumor and current status of CRT in Japan

Prospective trials[1–2] in patients with unresectable tumors have been conducted to compare CRT with RT or CT alone, and these studies have shown that CRT had a survival benefit over RT or CT alone. However, because the quality of these studies was poor and sample sizes were small, the results were not convincing. There have been no recent prospective trials using CRT for unresectable/recurrent tumor, and the role of CRT in this setting is therefore uncertain. Primary treatment for this category of tumor is CT, because recent advances in CT have resulted in improved survival. For instance, as a result of two randomized trials conducted in Japan (JCOG 9912[16] and SPIRITS[17]), S-1 plus cisplatin has become a standard regimen for unresectable/recurrent gastric cancer in this country. In both of these studies,[16,17] the median survival time (MST) for patients receiving S-1 was 11 months and for those receiving S-1 plus cisplatin, the MST was 13 months; the 2-year survival rates were 15% and 24%, respectively. The effectiveness of CRT in the treatment of unresectable/recurrent tumor should be evaluated by conducting phase I or II trials.

A phase II trial (Saikawa et al.[9]) has been conducted at Keio University in 13 patients with unresectable disease, using a combination of S-1 (60 mg/m$^2$ per day, days 1–21) and low-dose cisplatin (6 mg/m$^2$ per day, 5 days/week for 3 weeks) with concurrent RT (2 Gy × 5/week for 4 weeks, total 40 Gy) as a first-line treatment. (Table 4) The response rate was 76.9%, peritoneal dissemination disappeared in 3 of 3 patients, and improvement in quality of life (QOL) was obtained in 84.6%. Patients enrolled in the study represented a wide range of tumor stages; some of them underwent subsequent surgical resection and some patients had metastatic disease. Though survival data were not available, CRT may have the potential to make palliative surgical resection unnecessary.

**Table 4.** Current status of chemoradiotherapy for unresectable/recurrent gastric cancer in Japan

| |
|---|
| Unresectable cancer |
| Saikawa et al.[9], phase II trial for advanced cancer (first-line treatment) |
| S-1, 60 mg/m$^2$, days 1–21 |
| Cisplatin, 6 mg/m$^2$ per day, days 1–5, 8–12, 15–19 (5 days/week) |
| RT, 2 Gy · × 5/week for 4 weeks, total 40 Gy |
| Response rate, 77% (10 PR, 2 NC, 1 PD) |
| Primary, 63.8% (7 PR, 6 Nc) |
| Lymph node, 77% (10 PR, 3 NC) |
| Peritoneum, 100% (3 CR) |
| Improvement in QOL, 85% (11/13) |
| Recurrent cancer |
| Fujitani et al., pilot study for recurrent cancer (second- to fifth-line treatment): unpublished data |
| S-1, 40 mg/m$^2$, days 1–33 |
| docetaxel, 20 mg/m$^2$, days 1, 8, 15, 22, 29 |
| RT, 1.8 Gy × 5/week for 5 weeks, total 45 Gy |
| Response rate, 33% (3/9) |
| Alleviation of symptoms, 100% (6/6) |
| MST, 251 days |
| MMTG study group, phase I study (first- to second-line treatment) |
| Paclitaxel (50, 60, 70, 80) mg/m$^2$, days 1, 15, 29 |
| Cisplatin (20, 25) mg/m$^2$, days 1, 15, 29 |
| RT, 1.8 × 5/week for 5 weeks, total 45 Gy |
| Ongoing |

We conducted a pilot CRT study for recurrent tumor as second- to fifth-line treatment, the regimen of which was S-1 and weekly docetaxel with concurrent RT (45 Gy). The response rate was 33% (3/9 patients) and alleviation of symptoms was observed in 100% (6/6 patients). Toxicities were substantial; grade 3–4 leucopenia was observed in 22% of the patients and one treatment-related death (TRD) occurred. The Multi-modality therapy for gastric cancer (MMTG) study group have proposed a phase I trial of CRT (2004, Yoshikawa). In the trial, it is planned to escalate the dose of taxol (days 1, 15, 29) from 40 to 80 mg/m$^2$ with two different doses of cisplatin (20 or 25 mg/m$^2$) in conjunction with concurrent RT (1.8 Gy/day, 5 days/week for 5 weeks, total 45 Gy). Recruitment is ongoing for this trial.

## Summary

CRT has definite benefits in gastric cancer, with a high pCR rate and good local control, so that this modality should be introduced as a treatment option for Japanese patients. There is no rationale for using CRT in patients after D2 surgery in the adjuvant setting. Intensive adjuvant CT with S-1 plus cisplatin will be evaluated. CRT may be the best modality in the neoadjuvant setting for high-risk advanced tumors, such as type IV or large type III, N3/bulky N2 metastasis, or locally advanced (T4) tumors, or where there is esophageal invasion. The benefit of neoadjuvant S-1 plus cisplatin followed by postoperative S-1 will be evaluated in the phase III JCOG 0501 trial for large type III or type IV tumors. The role of neoadjuvant RT in addition to CT is yet to be clarified and we have to wait for the results of ongoing trials. We have little evidence to support the use of CRT as first-line treatment for unresectable/recurrent tumors; therefore, phase I/II trials should be conducted first to determine its potential benefits in this setting. However, our experience suggests that CRT may be suitable as second- or third-line treatment in such patients.

## References


1. Moertel CG, Childs DS Jr, ReitemeierRJ, et al. (1969) Combined 5-fluorouracil and supervoltage radiation therapy of locally unresectable gastrointestinal cancer. Lancet II:865–867
2. Schein P, Novak J (for GITSG) (1982) Combined modality therapy (XRT-chemo) versus chemotherapy alone for locally unresectable gastric cancer. Cancer Chemother Pharmacol 49:1771
3. Macdonald JS, Smalley SR, Benedetti J, et al. (2001) Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 345:725–730
4. Ajani JA, Mansfield PF, Janjan N, et al. (2004) Multi-institutional trial of preoperative chemoradiotherapy in patients with potentially resectable gastric carcinoma. J Clin Oncol 22:2774–2780
5. Ajani JA, Mansfield PF, Crane CH, et al. (2005) Paclitaxel-based chemoradiotherapy in localized gastric carcinoma: degree of pathologic response and not clinical parameters dictated patient outcome. J Clin Oncol 23:1237–1244
6. Ajani JA, Winter K, Okawara GS, et al. (2006) Phase II trial of preoperative chemoradiation in patients with localized gastric adenocarcinoma (RTOG 9904): Quality of combined modality therapy and pathologic response. J Clin Oncol 24:3953–3958
7. Ng K, Meyerhardt JA, Fuchs C (2007) Adjuvant and neoadjuvant approaches in gastric cancer. Cancer J 13:168–174
8. Abe M, Takahashi M, Ono K, et al. (1988) Japan gastric trials in intraoperative radiation therapy. Int J Radiat Oncol Biol Phys 15:1431–1433
9. Saikawa Y, Kiyota T, Nakamura R, et al. (2006) A recent trial of chemo-radiation with S-1 against gastric cancer. Jpn J Cancer Chemother 33 (Suppl I):99–105
10. Bonenkamp JJ, Hermans J, Sasako M, et al. (1999) Extended lymph-node dissection for gastric cancer. N Engl J Med 340:908–914
11. Wu C-W, Hsiung CA, Lo S-S, et al. (2006) Nodal dissection for patients with gastric cancer: a randomized controlled trial. Lancet Oncol 7:309–315
12. Sasako M, Sano T, Yamamoto A, et al. (2006) Randomized phase III trial of standard D2 versus D2 + para-aortic lymph node (PAN) dissection (D) for clinically M0 advanced gastric cancer: JCOG 9501. J Clin Oncol 24: 18S (abstract #LBA4015)
13. Cunningham D, Allum WH, Stenning SP, et al. (2006) Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 355:11–20
14. Sakuramoto S, Sasako M, Yamaguchi T, et al. (2007) Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med 357:1810–1820
15. Kim S, Lim DH, Lee J, et al. (2005) An observational study suggesting clinical benefit for adjuvant postoperative chemoradiation in a population of over 500 cases after gastric resection with D2 nodal dissection for adenocarcinoma of the stomach. Int J Radiat Oncol Biol Phys 63:1279–1285
16. Boku N, Yamamoto S, Shirao K, et al. (2007) Randomized phase III study of 5-fluorouracil (5-FU) alone versus combination of irinotecan and cisplatin (CP) versus S-1 alone in advanced gastric cancer (JCOG 9912). J Clin Oncol 25:18S (abstract # LBA4513)
17. Narahara H, Koizumi W, Hara T, et al. (2007) Randomized phase III study of S-1 + cisplatin in the treatment for advanced gastric cancer (the SPRITS trial) SPRITS: S-1 + cisplatin vs S-1 in RCT in the treatment for stomach cancer. J Clin Oncol 25:18S (abstract #4514)

World J Surg
DOI 10.1007/s00268-010-0914-5

World Journal of Surgery

# Influence of Bursectomy on Operative Morbidity and Mortality After Radical Gastrectomy for Gastric Cancer: Results of a Randomized Controlled Trial

**Hiroshi Imamura · Yukinori Kurokawa · Junji Kawada · Toshimasa Tsujinaka · Shuji Takiguchi · Yoshiyuki Fujiwara · Masaki Mori · Yuichiro Doki**



**Abstract**

*Background* Bursectomy, a procedure dissecting the peritoneal lining covering the pancreas and the anterior plane of the transverse mesocolon, has been commonly performed with radical gastrectomy for gastric cancer patients. Although possibly improving the prognosis of gastric cancers, adverse events related to bursectomy should be evaluated in prospective studies.

*Methods* This prospective randomized controlled trial was conducted by experienced surgeons in 11 Japanese institutions. Patients with T2 or T3 gastric adenocarcinoma were intraoperatively randomized to radical gastrectomy plus D2 lymphadenectomy either with or without bursectomy. Postoperative morbidity and mortality were compared between the two groups.

*Results* A total of 210 patients were assigned to the bursectomy group (104 patients) and the nonbursectomy group (106 patients) between July 2002 and January 2007. Background characteristics were well balanced. Intraoperative blood loss was greater in the bursectomy group than in the nonbursectomy group (median 475 vs. 350 ml, $p = 0.047$), whereas other surgical factors did not vary significantly. The overall morbidity rate was 14.3% (30 patients), the same for the two groups. Likewise, the incidence of major postoperative complications, including pancreatic fistula, anastomotic leakage, abdominal abscess, bowel obstruction, hemorrhage, and pneumonia, were not significantly different between the two groups. The medians of the amylase level of the drainage fluid on postoperative day 1 were similar for the two groups (median 282 vs. 314 IU/L, $p = 0.543$). The hospital mortality rate was 0.95%: one patient per group.

*Conclusions* Experienced surgeons could safely perform a D2 gastrectomy with an additional bursectomy without increased major surgical complications.

## Introduction

More than half of the new cases of gastric cancer occur in eastern Asia [1]. The surgical intervention for gastric cancers has rapidly developed in Japan. An extended radical lymphadenectomy, which is almost identical to the present D2 dissection, along with bursectomy was established as the standard treatment for advanced gastric cancers during the early 1960s [2, 3]. Bursectomy is a traditional surgical procedure to dissect the peritoneal lining covering the pancreas and the anterior plane of the transverse mesocolon with an omentectomy [4, 5]. This procedure is recommended in the Japanese Gastric Cancer Treatment Guidelines as part of the radical surgery for gastric cancer to remove micrometastases disseminated into the bursa omentalis [6]. As gastric cancer in the posterior wall sometimes shows peritoneal dissemination only in the bursa omentalis, its resection may improve survival [7].

On the other hand, a bursectomy causes some surgical stress when performed in addition to a D2 lymph node

H. Imamura
Department of Surgery, Sakai Municipal Hospital, Sakai, Japan

Y. Kurokawa (✉) · J. Kawada · S. Takiguchi · Y. Fujiwara · M. Mori · Y. Doki
Department of Gastroenterological Surgery, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan
e-mail: ykurokawa@gesurg.med.osaka-u.ac.jp

T. Tsujinaka
Department of Surgery, Osaka National Hospital, Osaka, Japan

Published online: 16 December 2010

dissection. Therefore, the possible increase in the incidence of postoperative complications, including pancreatic fistula formation, intestinal obstruction, and hemorrhage, may be concerning. As the safety of a D2 lymph node dissection is still controversial in Western countries [8, 9], we should also carefully evaluate the safety of bursectomy. To elucidate the safety and usefulness of the bursectomy, we conducted a multiinstitutional randomized controlled trial. We hereby present our operative morbidity and mortality data, the secondary endpoints of this trial. The final analysis of survival data is scheduled to take place in 2012.

## Patients and methods

### Patients

Patient eligibility criteria for this study were as follows: (1) histologically proven primary adenocarcinoma of the stomach; (2) a preoperative and intraoperative classification of T2N0, T3N0, T2N1, or T3N1 according to 13th edition of the Japanese Classification of Gastric Carcinoma [10]; (3) a lack of noncurative surgical factors except for positive lavage cytology; (4) no Borrmann type 4 (linitis plastica) cases; (5) no prior chemotherapy or radiation therapy; (6) ages 20 to 80 years with a performance status of 0 to 2 according to the Eastern Cooperative Oncology Group (ECOG) scale; (7) no history of gastrectomy or other malignancy during the last 5 years. All patients gave written informed consent before undergoing randomization.

When the surgeon confirmed the above eligibility criteria immediately after the initial laparotomy, patients were then intraoperatively randomized to the bursectomy group (a D2 gastrectomy with bursectomy) or the nonbursectomy group (without bursectomy). Randomizations were made by the minimization method according to sex, clinical T stage (cT2 vs. cT3), and gastrectomy (total vs. distal subtotal gastrectomy).

### Surgery

In both the bursectomy and nonbursectomy groups, the surgeon performed a total or distal subtotal gastrectomy and D2 lymph node dissection as a standard treatment for advanced gastric cancers [10]. With total gastrectomy for T2 or deeper tumors in the proximal third of the stomach, the spleen was removed in principle for splenic hilar lymphadenectomy. Pancreatectomy was confined to those patients whose pancreas was involved by tumor.

An omentectomy was performed for both groups in this study. In the bursectomy group, the peritoneal lining of the bursa omentalis was removed en bloc as much as possible from the anterior plane of the transverse mesocolon and the pancreas. In the caudal area of the bursa omentalis, the anterior lesion was removed with the minor omentum at the edge of the left lobe of the liver. The posterior and right-sided lesions were removed with lymph node dissection along the common hepatic artery (no. 8a), the splenic artery (no. 11p/d), the left gastric artery (no. 7), and in the hepatoduodenal ligament (no. 12a). As complete removal of the left side of the bursa omentalis did not allow a distal subtotal gastrectomy, pancreatic serosa was removed up to the proximal half of the splenic artery (no. 11p). For the transverse colon mesentery, the peritoneum was removed up to the left gastroepiploic artery (no. 4sb). In the nonbursectomy group, the right anterior surface of the transverse colon mesentery was partially removed around the root of the right gastroepiploic artery (no. 6). Only a small amount of peritoneum could be removed for lymph node dissection. Thus, the bursa omentalis peritoneal lining was preserved as much as possible in the nonbursectomy group. The type of reconstruction and the indication of prophylactic cholecystectomy were not specified in the protocol.

Patients were enrolled from 11 hospitals belonging to the Osaka University Clinical Research Group for Gastroenterological Surgery. More than 50 gastrectomies were performed each year in these 11 hospitals. All operations were performed or supervised by senior surgeons who were members of the Japanese Gastric Cancer Association. During the planning of the study, all participating surgeons reached an agreement concerning the technical details of bursectomy.

### Postoperative evaluation

Operative methods and pathology results were recorded according to the 13th edition of the Japanese Classification of Gastric Carcinoma [10]. The number of dissected lymph nodes was measured by pathology. Drainage fluid was collected via an operatively placed drain on postoperative day (POD) 1 for measuring the amylase level. The six Representative data for the six major morbidities—pancreatic fistula, anastomotic leakage, abdominal abscess, bowel obstruction, hemorrhage, pneumonia—were prospectively collected. A pancreatic fistula was defined by a drainage output on or after POD 5 with an amylase content more than three times the upper normal serum value. Pneumonia, anastomotic leakage, abdominal abscess, and bowel obstruction were diagnosed radiologically or clinically. Postoperative hemorrhage requiring a transfusion was recorded as morbidity. Any other complications requiring pharmacologic or surgical treatment were recorded on a free format. Operative morbidity until 3 months after surgery was also analyzed in this study. Operating time, blood loss, duration of hospital stay after surgery, and reoperation details were also recorded. Hospital mortality

was defined as postoperative death of any cause within 30 days or death during the same hospitalization.

Patients were followed every 3 months until 5 years after the operation. Adjuvant therapy was not permitted before a recurrence of cancer.

### Statistical Analysis

The primary endpoint was overall survival (OS). Secondary endpoints were recurrence-free survival, operative morbidity, and POD 1 drainage amylase levels. We planned initially to recruit 200 patients, with an alpha error of 0.1 and statistical power of 80%. This allowed detection of a 10% margin of noninferiority for the nonbursectomy group under the estimation of a 60% 5-year OS in the bursectomy group. The projected accrual period and follow-up period were 3 years and 5 years, respectively. After registration of 204 patients, we amended the sample size and analysis to correct the estimation of the 5-year OS in the bursectomy group as 75% and to reduce alpha error. The amended sample size was 464, with an alpha error of 0.05 and statistical power of 80%, with an 8-year accrual period (total) and 5-year follow-up.

In January 2007, the positive result of a large-scale randomized controlled trial to evaluate adjuvant S-1 chemotherapy for stage II/III gastric cancer patients was reported [11, 12]. Since then, adjuvant S-1 chemotherapy has been a new standard treatment for stage II/III gastric cancer patients in Japan. However, because any adjuvant treatment including S-1 was not allowed after surgery in our study, we decided to close the accrual of our study in January 2007.

The operative morbidity and mortality rates were based on the proportion of the number of cases divided by all registered patients based on the intention-to-treat principle. The differences in proportion between the two groups were evaluated using Fisher's exact test or chi-squared test. The differences of continuous variables, including age, body mass index, tumor size, operating time, blood loss, and the number of dissected lymph nodes for the two groups were tested with a Mann-Whitney U-test. All $p$ values were two-sided, and statistical analysis was done using SPSS Statistics software, version 17.0 (SPSS, Chicago, IL, USA).

## Results

### Patients and surgery

Between July 2002 and January 2007, a total of 210 patients were randomly divided into 104 in the bursectomy group and 106 in the nonbursectomy group (Fig. 1). One patient in the bursectomy group did not undergo bursectomy, and one in the nonbursectomy group underwent bursectomy. Most of the baseline characteristics were well balanced (Table 1). The bursectomy group had slightly older patients than the nonbursectomy group (median 65 vs. 63 years, $p = 0.099$). The number of patients with pathologically positive nodes was slightly higher in the bursectomy group than in the nonbursectomy group (52.9% vs. 43.4%, $p = 0.214$).

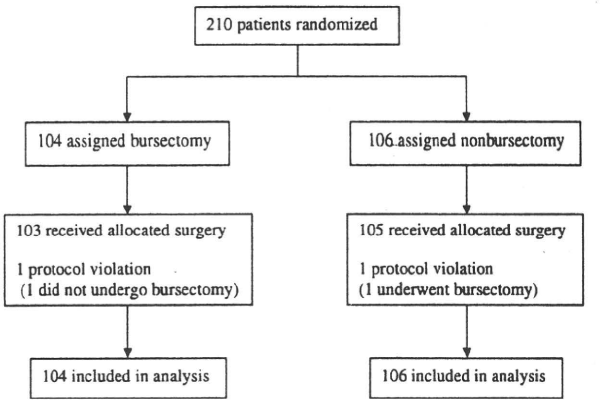



**Fig. 1** CONSORT flowchart for patients

The operative details are shown in Table 2. A total gastrectomy was performed on 22 (21.2%) patients in the bursectomy group and on 27 (25.5%) patients in the nonbursectomy group. About one-half of patients in each of the two groups underwent a Roux-en-Y reconstruction procedure. A combined resection of other organs was performed for 103 patients in total. The resected organs were the gallbladder in 98 patients, spleen in 26 patients, part of the pancreas in 1 patient, the colon in 1 patient, the left adrenal gland in 1 patient, and the diaphragm in 1 patient. It was of note that although the difference was not statistically significant the number of patients with a combined resection was greater in the nonbursectomy group than in the bursectomy group (42.3 vs. 55.7%, $p = 0.055$). When we evaluated the operating time after dividing the patients into two subgroups, either with or without a combined resection of other organs, the bursectomy required a longer operating time (median 27 min in patients with a combined resection, 26 min in patients without a combined resection). The amount of blood loss significantly increased in the bursectomy group compared to the nonbursectomy group (median 475 vs. 350 ml, $p = 0.047$). There was no significant difference between the two groups regarding the number of dissected lymph nodes.

### Operative morbidity and mortality

The overall operative morbidity rate was 14.3% (30 patients), which was the same in the two groups (Table 3). Prespecified complications, including pancreatic fistula, anastomotic leakage, abdominal abscess, bowel obstruction,

**Table 1** Patient and tumor characteristics

| Characteristic | Bursectomy ($n = 104$) | Nonbursectomy ($n = 106$) | $p$* |
|---|---|---|---|
| Age (years) | | | 0.099 |
| Median | 65 | 63 | |
| Range | 31–79 | 34–78 | |
| Sex | | | 0.761 |
| Male | 73 | 77 | |
| Female | 31 | 29 | |
| Body mass index | | | 0.653 |
| Median | 22.3 | 22.5 | |
| Range | 15.7–28.9 | 15.6–29.4 | |
| Tumor size (cm) | | | 0.311 |
| Median | 4.3 | 4.5 | |
| Range | 0.9–11.0 | 1.5–12.0 | |
| Histological type | | | 0.784 |
| Differentiated | 47 | 50 | |
| Undifferentiated[a] | 57 | 56 | |
| Clinical T stage[b] | | | 0.572 |
| cT2 | 61 | 67 | |
| cT3 | 43 | 39 | |
| Clinical N stage[b] | | | 1.000 |
| cN0 | 59 | 61 | |
| cN1 | 45 | 45 | |
| Pathologic T stage[b] | | | 0.902 |
| pT1 | 17 | 19 | |
| pT2 | 62 | 64 | |
| pT3-4 | 25 | 23 | |
| Pathologic N stage[b] | | | 0.119 |
| pN0 | 49 | 60 | |
| pN1 | 37 | 24 | |
| pN2-3 | 18 | 22 | |
| Residual tumor | | | 1.000 |
| R0 | 101 | 102 | |
| R1 | 3 | 4 | |

* The $p$ values were calculated by Fisher's exact test for sex, histological type, clinical T stage, clinical N stage, and residual tumor; by the chi-squared test for pathologic T stage and pathologic N stage; and by the Mann–Whitney $U$-test for age, body mass index, and tumor size

[a] Undifferentiated type included one endocrine cell carcinoma case in the nonbursectomy group

[b] T stage and N stage were according to the 13th edition of the Japanese Classification of Gastric Carcinoma

**Table 2** Profile of surgical treatment

| Treatment | Bursectomy ($n = 104$) | Nonbursectomy ($n = 106$) | $p$* |
|---|---|---|---|
| Gastrectomy | | | 0.515 |
| Total | 22 | 27 | |
| Distal subtotal | 82 | 79 | |
| Reconstruction method | | | 0.705 |
| Roux-en-Y | 48 | 55 | |
| Billroth I | 54 | 49 | |
| Other[a] | 2 | 2 | |
| Combined resection of other organs | | | 0.055 |
| Present | 44 | 59 | |
| Gallbladder | 41 | 57 | |
| Spleen | 12 | 14 | |
| Other[b] | 1 | 2 | |
| Absent | 60 | 47 | |
| Operating time (min) | | | 0.368 |
| Median | 222 | 221 | |
| Range | 134–488 | 111–360 | |
| Blood loss (ml) | | | 0.047 |
| Median | 475 | 350 | |
| Range | 80–3970 | 55–2901 | |
| No. of dissected lymph nodes | | | 0.417 |
| Median | 38 | 37 | |
| Range | 11–98 | 7–97 | |

* $p$ values were calculated by Fisher's exact test for gastrectomy and combined resection of other organs (present or absent); by chi-squared test for the reconstruction method; and by the Mann–Whitney $U$-test for operating time, blood loss, and the number of dissected lymph nodes

[a] Others included one Billroth II method and one intestinal interposition method in the bursectomy group and two Billroth II methods in the nonbursectomy group

[b] Others included one adrenal gland in the bursectomy group and one pancreas and one diaphragm in the nonbursectomy group

**Table 3** Postoperative morbidity

| Morbidity | Bursectomy ($n = 104$) | Nonbursectomy ($n = 106$) | $p$* |
|---|---|---|---|
| Any complication | 15 | 15 | 1.000 |
| Pancreatic fistula | 3 | 7 | 0.332 |
| Anastomotic leakage | 4 | 3 | 0.720 |
| Abdominal abscess | 3 | 8 | 0.214 |
| Bowel obstruction | 2 | 1 | 0.620 |
| Hemorrhage | 1 | 0 | 0.495 |
| Pneumonia | 1 | 1 | 1.000 |

* The $p$ values were calculated by Fisher's exact test

hemorrhage, and pneumonia, did not significantly differ between the two groups. Among the 10 patients with a pancreatic fistula, 6 underwent splenectomy, but no patients underwent pancreaticosplenectomy. Ten patients suffered from other complications, including two cases of chylous lymphorrhea, two of delayed gastric emptying without obstruction, and one case of afferent loop syndrome, acute cholecystitis, acute enteritis, arteriosclerosis obliterans of the leg, drug-induced hepatitis, and anastomotic stricture. The incidence of these miscellaneous complications tended

to be more frequent in the bursectomy group than in the nonbursectomy group (7.7 vs. 1.9%, $p = 0.057$). The median amylase levels in the drainage fluid on POD 1 were 282 IU/L in the bursectomy group and 314 IU/L in the nonbursectomy group ($p = 0.543$). Reoperation was required in four patients (1.9%): two for intestinal obstruction, one for afferent loop syndrome in the bursectomy group, and one for anastomotic leakage in the nonbursectomy group. The median hospital stay after surgery was 16 days in the bursectomy group and 15 days in the nonbursectomy group ($p = 0.744$).

There were two hospital deaths (0.95%). One patient in the bursectomy group and one patient in the nonbursectomy group died of sepsis after anastomotic leakage and pancreatic fistula formation, respectively. All other patients recovered from surgery and were discharged from the hospital.

## Discussion

Two factors are necessary for bursectomy to be accepted as a standard treatment for advanced gastric cancers: safety and oncologic benefit. Only a randomized clinical trial can scientifically evaluate this proposition, and we are the first worldwide to conduct such a trial. This article is an early report of this trial with respect to operative safety. We found that overall morbidity and mortality were equivalent with and without bursectomy. Although the amount of surgical blood loss was significantly increased with bursectomy, overall we concluded that this procedure is safe and acceptable.

The safety of surgical treatments strongly depends on the surgeon's experience. Specific training is required to perform any surgical procedure, particularly when it is done for cancer treatment. There have been clinical trials studying the extent of lymph node dissection during gastric surgery. Two European randomized trials comparing D1 with D2 lymphadenectomy concluded that D2 was not acceptable as a standard treatment because D2 was associated with higher morbidity and mortality than D1 [8, 9]. On the other hand, two randomized trials comparing D1 with D2 and D2 with D3 lymphadenectomy in eastern Asia demonstrated that both D2 and D3 gastrectomy could be performed with low operative risk [13, 14]. This finding can be explained by the high volume of gastric cancer patients treated at that hospital and the high prevalence of gastric cancer in eastern Asia. In this study, all the patients were enrolled from an institution in which more than 50 gastrectomies were performed each year. In our trial the surgical procedures being performed by experienced surgeons accounted for the low mortality rates (0.95%) and low morbidity rates (14.3%).

Among various adverse events after surgery, we were concerned about the increased incidence of pancreatic fistulas after bursectomy because bursectomy requires resection of the capsule covering the pancreas [15]. However, we did not observe a significant increase in the incidence of pancreatic fistulas or inappropriate amylase levels in the postoperative drainage fluid, a surrogate marker of a pancreas fistula. This suggests that a pancreatic fistula is not caused by removal of a pancreatic capsule but may be caused by lymph node dissection adjacent to the pancreas parenchyma.

The next concern included the possibility of adhesion formation. Intestinal obstruction is the representative symptom of adhesion. In this study, two bursectomy patients and one nonbursectomy patient suffered from postoperative bowel obstruction, but there was no significant difference between the two groups. As 3 months' observation after surgery was not enough to evaluate the incidence of intestinal obstruction, a longer observation is necessary to draw a conclusion. Adhesion to the mesocolon and pancreas may cause specific local symptoms, such as delayed gastric emptying or afferent loop syndrome. It is of note that both delayed gastric emptying (two patients) and afferent loop syndrome (one patient) were observed only in the bursectomy group. Although this also did not reach statistical significance, careful observation is required in a larger cohort study.

In general, omentectomy and bursectomy are simultaneously performed for the same purpose, but their clinical pictures are somehow different. As the great omentum has numerous milky spots, which absorb ascites and actively incorporate cancer cells, peritoneal metastasis is frequently observed [16]. On the other hand, bursa omentalis, which is a semi-closed cavity, allows exfoliated cancer cells to remain. As for the surgical aspects, omentectomy is not difficult and does not increase the operating time or the blood loss. In contrast, the bursectomy technique is complicated and increases the operating time and bleeding. Considering the balance between the risk and benefit of each surgical procedure, we performed an omentectomy for all patients and randomly assigned each case to either with or without bursectomy. If we cannot find a benefit of bursectomy in this trial, we should elucidate the significance of omentectomy in the next step.

## Conclusions

This study showed that experienced surgeons could safely perform a D2 gastrectomy with bursectomy. Although bursectomy resulted in more blood loss, the major operative complications and hospital deaths were not increased. Regarding the survival benefit of this procedure, we must

wait for the results of the final analysis when the data have matured sufficiently.

**Acknowledgments** We thank Professor Kunio Okajima for helpful advice and Dr. Tomoyuki Sugimoto for statistical analysis of this study.

**Conflict of interest** The authors declare no conflicts of interest.

## References

1. Kelley JR, Duggan JM (2003) Gastric cancer epidemiology and risk factors. J Clin Epidemiol 56:1–9
2. Jinnai D (1967) Theory and practice of the extended radical operation for gastric cancer. Rinsho Geka 22:19–24 (in Japanese)
3. Maruyama K, Okabayashi K, Kinoshita T (1987) Progress in gastric cancer surgery in Japan and its limits of radicality. World J Surg 11:418–425
4. Groves EWH (1910) On the radical operation for cancer of the pylorus. BMJ 12:366–370
5. Oglivie WH (1939) Cancer of the stomach. Surg Gynecol Obstet 68:295–305
6. Japanese Gastric Cancer Association (2004) Gastric cancer treatment guidelines. Kanehara, Tokyo (in Japanese)
7. Hagiwara A, Sawai K, Sakakura C et al (1998) Complete omentectomy and extensive lymphadenectomy with gastrectomy improves the survival of gastric cancer patients with metastases in the adjacent peritoneum. Hepatogastroenterology 45:1922–1929
8. Bonenkamp JJ, Hermans J, Sasako M et al (1999) Extended lymph-node dissection for gastric cancer. N Engl J Med 340: 908–914
9. Cuschieri A, Weeden S, Fielding J et al (1999) Patient survival after D1 and D2 resections for gastric cancer: long-term results of the MRC randomized surgical trial. Br J Cancer 79:1522–1530
10. Japanese Gastric Cancer Association (1998) Japanese classification of gastric carcinoma: 2nd English edition. Gastric Cancer 1:10–24
11. Sasako M, Yamaguchi T, Kinoshita T et al (2007) Randomized phase III trial comparing S-1 monotherapy versus surgery alone for stage II/III gastric cancer patients (pts) after curative D2 gastrectomy (ACTS-GC study) (abstract). In: Proceedings of the American Society of Clinical Oncology (gastrointestinal cancers symposium) (abstract 8)
12. Sakuramoto S, Sasako M, Yamaguchi T et al (2007) Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med 357:1810–1820
13. Wu CW, Hsiung CA, Lo SS et al (2006) Nodal dissection for patients with gastric cancer: a randomised controlled trial. Lancet Oncol 7:309–315
14. Sasako M, Sano T, Yamamoto S et al (2008) D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer. N Engl J Med 359:453–462
15. Herbella FA, Tineli AC, Wilson JL Jr et al (2008) Gastrectomy and lymphadenectomy for gastric cancer: is the pancreas safe? J Gastrointest Surg 12:1912–1914
16. Hagiwara A, Takahashi T, Sawai K et al (1993) Milky spots as the implantation site for malignant cells in peritoneal dissemination in mice. Cancer Res 53:687–692

Experimental Chemotherapy

Chemotherapy

Chemotherapy 2010;56:436–443
DOI: 10.1159/000317762

Received: February 2, 2010
Accepted after revision: May 30, 2010
Published online: November 17, 2010

# Effect of S-1 Adjuvant Chemotherapy on Survival following Recurrence and Efficacy of First-Line Treatment in Recurrent Gastric Cancer

Hiroko Hasegawa[a] Kazumasa Fujitani[b] Yukinori Kurokawa[b] Motohiro Hirao[b]
Shoichi Nakazuru[a] Eiji Mita[a] Toshimasa Tsujinaka[b]

Departments of [a]Gastroenterology and [b]Surgery, National Osaka Medical Center, Osaka, Japan

**Key Words**

Adjuvant chemotherapy · S-1 · Recurrent gastric cancer · Overall survival · Efficacy of chemotherapy

**Abstract**

***Background:*** As S-1 monotherapy has recently become the standard adjuvant regimen for stage II-III gastric cancer patients after curative gastrectomy in Japan, the question whether adjuvant S-1 affects the subsequent clinical course of relapsed patients has attracted great concern. ***Patients and Methods:*** We retrospectively evaluated the effect of adjuvant S-1 on survival following recurrence and efficacy of first-line treatment in patients with recurrent gastric cancer after curative gastrectomy. A total of 89 patients were evaluated. Thirty patients received adjuvant S-1 (cohort A), 10 patients were given adjuvant chemotherapy with other oral 5-FU agents (cohort B) and 49 patients received no adjuvant chemotherapy (cohort C). ***Results:*** Median survival time following recurrence was 287 days in cohort A, 451 days in B and 547 days in C, with a significant difference between A and C ($p = 0.0034$). Response rates of the first-line chemotherapy after recurrence were 6.7, 30.0 and 42.9% in cohorts A, B and C, respectively, with a significant difference between A and C ($p = 0.0007$). On multivariate analysis, S-1 adjuvant chemotherapy was independently associated with poor prognosis after recurrence (hazard ratio 2.64). ***Conclusion:*** S-1 adjuvant chemotherapy significantly reduced survival and response to first-line chemotherapy following recurrence in patients with recurrent gastric cancer.



## Introduction

Although several meta-analyses have suggested a survival benefit provided by adjuvant chemotherapy for gastric cancer [1–6], there have been only a few treatments with their efficacy established in large clinical trials. Postoperative radiotherapy with 5-FU plus leucovorin has become a standard adjuvant therapy in the US [7], while peri-operative triplet regimen with epirubicin, cisplatin and 5-FU is standard in the UK [8]. Recently in Japan, the ACTS-GC trial has verified the efficacy of S-1 adjuvant chemotherapy after curative gastrectomy for stage II-III disease [9]. However, around 30% of patients still develop recurrence afterwards despite adjuvant S-1. As the number of patients relapsing after S-1 adjuvant chemotherapy increases, it becomes of great concern whether adjuvant S-1 affects the subsequent clinical behavior of the recurrent disease.

This retrospective study was conducted to evaluate the effect of S-1 adjuvant chemotherapy, in comparison with other 5-FU agents or no adjuvant chemotherapy, on sur-

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com


0009–3157/10/0566–0436$26.00/0

Accessible online at:
www.karger.com/che

Kazumasa Fujitani, MD
Department of Surgery, National Osaka Medical Center
2-1-14 Hoenzaka
Chuo-ku, Osaka 540-0006 (Japan)
Tel. +81 6 6942 1331, Fax +81 6 6943 6467, E-Mail fujitani@onh.go.jp

vival following recurrence and efficacy of first-line chemotherapy given at the time of relapse in patients with recurrent gastric cancer after curative gastrectomy.

## Patients and Methods

*Patients*

A total of 95 patients with recurrent gastric cancer after curative gastrectomy were found at our institution between April 1999 and October 2008. Among them, 89 patients enrolled in this retrospective study fulfilled the following criteria: (1) histologically proven recurrent gastric adenocarcinoma; (2) stage II, III or IV primary disease without any distant metastasis in accordance with the guidelines of the Japanese Gastric Cancer Association [10]; (3) either adjuvant chemotherapy with S-1 or other oral 5-FU agents (UFT or 5′-FUDR) lasting more than 4 weeks or no adjuvant treatment; (4) performance status of 2 or less on the Eastern Cooperative Oncology Group scale; (5) adequate bone marrow function (white blood cell count 4,000–12,000/mm$^3$, platelet count ≥100,000/mm$^3$ and hemoglobin ≥8.0 g/dl), hepatic function (total bilirubin ≤1.5 mg/dl, serum transaminases ≤100 μ/l) and renal function (serum creatinine ≤ the upper institutional limit); (6) no other severe medical conditions; (7) no other concurrent active malignancy.

*Overall Survival, Efficacy of First-Line Chemotherapy and Statistics*

Overall survival (OS) after recurrence was defined as the time from the date of recurrence to the date of death from any cause or the last follow-up. OS was calculated using the Kaplan-Meier method and compared with the log-rank test. Univariate and multivariate analyses were performed by the Cox proportional hazards model to identify variables independently associated with poor prognosis after recurrence.

During the first-line chemotherapy after recurrence, each patient with a measurable lesion was assessed for an objective response to treatment according to the Response Evaluation Criteria in Solid Tumors [11] with computed tomography scans performed every 2 to 3 months until disease progression. Disease control rate (DCR) represented the percentage of patients with complete response, partial response or stable disease (SD). Patients only with nonmeasurable lesions were evaluated as stable disease if neither complete disappearance (complete response) nor obvious progression of the recurrent disease were observed on computed tomography scans.

Differences in proportion were evaluated with the $\chi^2$ test and the differential significance of age was estimated by the Kruskal-Wallis test. Statistical results were considered to be significant with a p value of less than 0.05.

## Results

*Patient Characteristics*

Eighty-nine patients were categorized into the 3 cohorts shown in table 1. Thirty patients in cohort A, 18 males and 12 females with a median age of 62.5 years (range: 32–83), received S-1 adjuvant chemotherapy. S-1 was given orally using a standard dose and schedule (80 mg/m$^2$/day, for 28 consecutive days followed by a 14-day rest, repeated for 1 year) [9]. Nine patients completed the planned 1-year administration of adjuvant S-1, while 11 patients discontinued the treatment within the first 6 months and 10 patients in the second 6 months after the initiation of S-1 adjuvant chemotherapy. The reasons for treatment withdrawal were treatment toxicity in 1, and recurrent disease in 20 patients. The median duration of adjuvant S-1 administration was 211 days. In cohort B, 10 patients, 6 males and 4 females with a median age of 63.0 years (range: 35–78), were given adjuvant chemotherapy with oral 5-FU agents other than S-1. UFT (a combination of uracil and tegafur at a molar ratio of 4:1) was administered at a dose of 400 mg/body/day in 6 patients and 5′-DFUR (5′-deoxy-5-fluorouridine) at a dose of 800 mg/body/day in 4 patients. Two patients completed the planned 1-year administration of adjuvant UFT/5′-DFUR, while 3 patients discontinued the treatment within the first 6 months and 5 patients in the second 6 months after the initiation of adjuvant chemotherapy. The rea-

**Table 1.** Patient characteristics

| | Cohort A S-1 adjuvant | Cohort B oral 5-FU | Cohort C no adjuvant | p value |
|---|---|---|---|---|
| Patients | 30 | 10 | 49 | |
| Gender | | | | 0.5254 |
| Male | 18 | 6 | 35 | |
| Female | 12 | 4 | 14 | |
| Age, years | | | | 0.8537 |
| Median | 62.5 | 63 | 59 | |
| Range | 32–83 | 35–78 | 42–84 | |
| Histology (Lauren's) | | | | 0.841 |
| Intestinal | 9 | 4 | 17 | |
| Diffuse | 21 | 6 | 32 | |
| Stage | | | | 0.0053 |
| II | 2 | 4 | 11 | |
| III | 13 | 5 | 32 | |
| IV | 15 | 1 | 6 | |
| Measurable lesions | | | | 0.6584 |
| Present | 19 | 6 | 26 | |
| Absent | 11 | 4 | 23 | |
| Metastatic sites | | | | 0.2531 |
| 1 | 25 | 10 | 45 | |
| ≥2 | 5 | 0 | 4 | |
| DFI | | | | 0.105 |
| <1 year | 19 | 5 | 19 | |
| ≥1 year | 11 | 5 | 30 | |

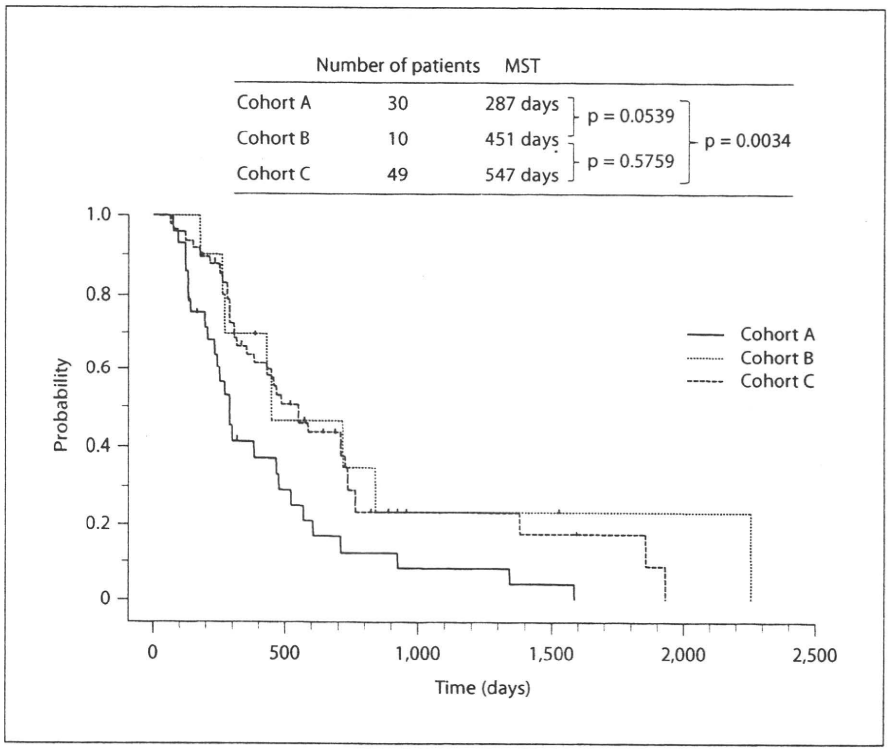



**Fig. 1.** OS after recurrence.

sons for treatment withdrawal were patient refusal in 1 and recurrent disease in 7 patients. The median duration of adjuvant 5-FU agent administration was 180 days. Forty-nine patients in cohort C, 35 males and 14 females with a median age of 59.0 years (range: 42–84), received no adjuvant chemotherapy. Histologically, around one third of patients had intestinal-type adenocarcinoma and two thirds had diffuse-type adenocarcinoma in each cohort. As for the initial stage of the primary tumor after curative gastrectomy, stage IV disease was significantly more frequent in cohort A than in the other cohorts (p = 0.0053). A measurable recurrent lesion was seen in 50–60% of each cohort and multiple metastatic sites were present in 10% of all patients. The disease-free interval (DFI), which was defined as the time from the date of surgery to the date of recurrence, was less than 1 year in approximately 40–60% of patients in either cohort.

*Overall Survival*

OS after recurrence was compared among the three cohorts. After a median follow-up time of 380 days from the date of recurrence (319 days in 71 dead patients and 560 days in 18 alive patents), the median survival time (MST) was 287 days in cohort A, 451 days in B and 547 days in C. OS was significantly shorter in cohort A than in cohort C (p = 0.0034), while there was no significant difference between cohorts B and A or C, as shown in figure 1. In cohort A, the duration of S-1 adjuvant chemotherapy was <6 months in 11 patients, 6 to <12 months in 10 and 12 months in 9. No significant difference in OS (MST, 246 vs. 287 vs. 464 days; p = 0.4963) was observed according to the duration of S-1 adjuvant chemotherapy, as shown in figure 2.

*Efficacy of First-Line Chemotherapy*

Regimens of the first-line chemotherapy delivered after recurrence are shown in table 2. Nine patients (30.0%) in cohort A received S-1-based therapy (S-1 monotherapy [12, 13] in 3, S-1 plus cisplatin [14] in 3, S-1 plus irinotecan [15] in 3, S-1 plus paclitaxel [16] in 0), although 9 patients were treated with paclitaxel monotherapy administered in a weekly fashion [17] and 12 patients with irinotecan-based therapy (irinotecan monotherapy [18] in 5, irinotecan plus cisplatin [19] in 7). In cohort B, 5 patients (50.0%) received S-1-based therapy, with 4 patients being treated with paclitaxel monotherapy and 1 patient with irinotecan plus cisplatin. In cohort C, 42 patients (85.7%) received S-1-based therapy, 4 patients were given paclitaxel monotherapy and 3 patients were given irinotecan plus cisplatin. It seemed inevitable for various regimens to

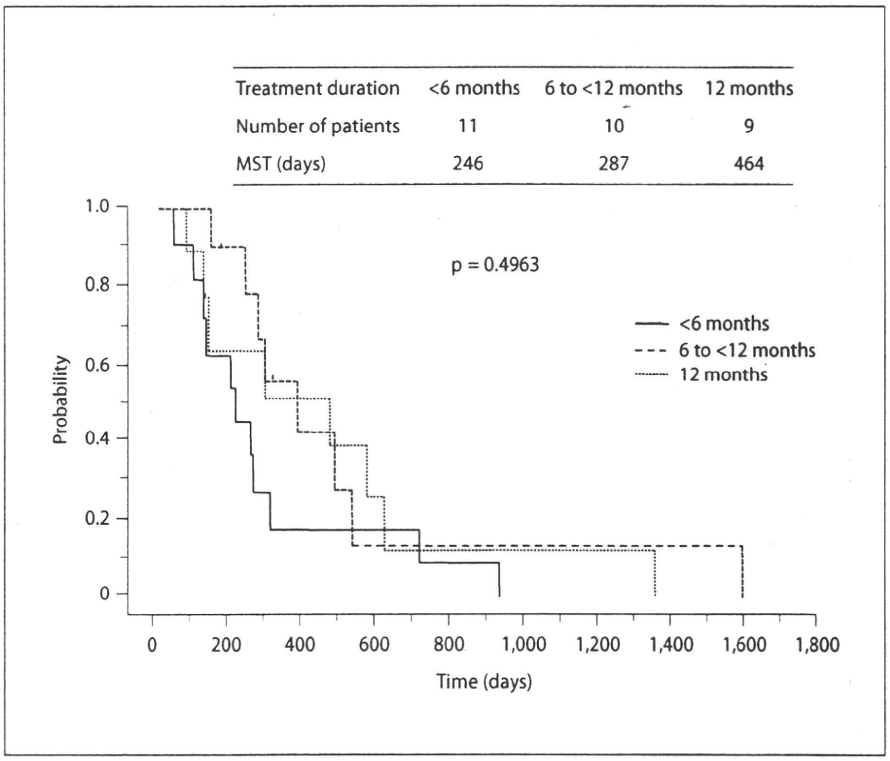



**Fig. 2.** OS according to the duration of S-1 adjuvant chemotherapy.

**Table 2.** Regimens of first-line chemotherapy after recurrence

| | Cohort A (n = 30 ) | Cohort B (n = 10) | Cohort C (n = 49) |
|---|---|---|---|
| S-1-based therapy | 9 | 5 | 42 |
| S-1 monotherapy | 3 | 3 | 26 |
| S-1 + cisplatin | 3 | 0 | 4 |
| S-1 + irinotecan | 3 | 1 | 7 |
| S-1 + paclitaxel | 0 | 1 | 5 |
| Weekly paclitaxel | 9 | 4 | 4 |
| Irinotecan-based therapy | 12 | 1 | 3 |
| Irinotecan monotherapy | 5 | 0 | 0 |
| Irinotecan + cisplatin | 7 | 1 | 3 |

have been given as the first-line treatment because it was obscure whether non-S-1-based therapy was more appropriate for patients relapsed after adjuvant S-1 or which should be chosen as a non-S-1 agent between paclitaxel and irinotecan for patients with recurrent gastric cancer. However, there was a tendency to prefer choosing S-1-based therapy as the first-line treatment after recurrence in cohort C, while non-5-FU regimens were more likely to be chosen in cohorts A and B. The best response to the first-line chemotherapy after recurrence was compared among these 3 cohorts, as shown in table 3. Response rates (RR) were 6.7% [95% confidence interval (CI) 0.8–22.1], 30.0% (95% CI 6.7–65.3), and 42.9% (95% CI 28.8–57.8) in cohorts A, B and C, respectively, with a significant difference between A and C (p = 0.0007). DCR were 50.0% (95% CI 31.3–68.7), 80.0% (95% CI 44.4–97.5) and 89.8% (95% CI 77.8–96.6) in cohorts A, B and C, respectively, with a significant difference between A and C (p = 0.0001).

*Prognostic Factors for OS*

The results of univariate and multivariate analyses of various factors, such as gender, age, histology, initial stage and presence of measurable lesion, number of metastatic sites, DFI and type of adjuvant chemotherapy for OS following recurrence are summarized in table 4. Among these, absence of a measurable lesion [hazard ratio 2.18 (95% CI 1.28–3.72)], presence of multiple metastatic sites [hazard ratio 2.89 (95% CI 1.28–6.52)] and S-1 adjuvant chemotherapy [hazard ratio 2.64 (95% CI 1.35–4.75)] were identified as significant independent factors for poor prognosis after recurrence.

**Table 3.** Efficacy of first-line chemotherapy

| | CR | PR | SD | PD | Total | RR, % | DCR, % |
|---|---|---|---|---|---|---|---|
| Cohort A | 0 | 2 | 13 | 15 | 30 | 6.7 (0.8–22.1) | 50 (31.3–68.7) |
| Cohort B | 2 | 1 | 5 | 2 | 10 | 30 (6.7–65.3) | 80 (44.4–97.5) |
| Cohort C | 4 | 17 | 23 | 5 | 49 | 42.9 (28.8–57.8) | 89.8 (77.8–96.6) |

Figures in parentheses are 95% CI.

**Table 4.** Prognostic factors for OS

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | patients | MST, days | p | hazard ratio | 95% CI | p |
| Gender | | | | | | |
| Male | 59 | 466 | 0.4212 | | | 0.791 |
| Female | 30 | 303 | | 1.082 | 0.606–1.930 | |
| Age, median 61 | | | | | | |
| ≥61 | 46 | 455 | 0.5071 | | | 0.91 |
| <61 | 43 | 446 | | 0.969 | 0.559–1.680 | |
| Histology | | | | | | |
| Intestinal | 30 | 455 | 0.5388 | | | 0.948 |
| Diffuse | 59 | 446 | | 0.981 | 0.556–1.733 | |
| Stage | | | | | | |
| II | 17 | 304 | 0.4825 | 1.115 | 0.444–2.800 | 0.744 |
| III | 50 | 455 | | 1.274 | 0.667–2.432 | |
| IV | 22 | 479 | | | | |
| Measurable lesion | | | | | | |
| Present | 51 | 547 | 0.0243 | | | 0.004 |
| Absent | 38 | 285 | | 2.181 | 1.279–3.720 | |
| Metastatic sites | | | | | | |
| 1 | 80 | 455 | 0.0154 | | | 0.011 |
| ≥2 | 9 | 268 | | 2.89 | 1.281–6.524 | |
| DFI | | | | | | |
| <1 year | 43 | 351 | 0.365 | 1.349 | 0.786–2.315 | 0.277 |
| ≥1 year | 46 | 521 | | | | |
| Adjuvant chemotherapy | | | | | | |
| None | 49 | 547 | 0.0061 | | | 0.008 |
| S-1 | 30 | 287 | | 2.635 | 1.346–4.747 | |
| Oral 5-FU | 10 | 451 | | 0.98 | 0.422–2.274 | |

## Discussion

Although adjuvant chemotherapy with S-1 has recently become the standard treatment for stage II-III gastric cancer patients after curative gastrectomy in Japan based on the result of the ACTS-GC trial [9], nearly 30% of patients still relapse, despite the adjuvant S-1 treatment. Since the total number of patients with recurrence after adjuvant S-1 is increasing, it is of great concern to discern whether adjuvant S-1 affects the subsequent clinical course of the patients after recurrence. We, therefore, retrospectively evaluated the effect of adjuvant S-1 on survival following recurrence and the efficacy of first-line chemotherapy given at the time of relapse in patients with recurrent gastric cancer.

As shown in figure 1, patients initially treated with adjuvant S-1 had shorter survival following the recurrence than those receiving no adjuvant treatment (MST 287 vs.

547 days, p = 0.0034). Similarly, adjuvant chemotherapy was reported to have a negative impact on outcome after recurrence in other types of cancer such as colon and breast [20, 21]. As for the results of subset analysis of cohort A shown in figure 2, there may be some controversies. MST of the patients who relapsed after completion of 12 months of S-1 adjuvant chemotherapy was 464 days, equivalent to that of 451 days in cohort B. Although the duration of S-1 adjuvant chemotherapy showed no effect on OS after recurrence, this lack of statistical difference between the subgroups might be due to the small sample size. However, at least, the patients who discontinued S-1 adjuvant chemotherapy within 12 months because of recurrence were very unlikely to be salvaged by the additional chemotherapy given at the time of relapse. Although there was an imbalance of initial stage of the primary tumor between cohorts A and C, as shown in table 1, MSTs at stage II-III and IV in cohort A were 237 and 479 days, respectively, while they were 588 and 290 days in cohort C, respectively, with no significant difference between stage II-III and IV. Furthermore, on multivariate analysis in table 4, S-1 adjuvant chemotherapy but not initial stage was confirmed as an independent prognostic factor for OS after recurrence. Absence of a measurable lesion and presence of multiple metastatic sites also significantly correlated with inferior survival on multivariate analysis. MSTs of patients whose metastatic lesions involved the peritoneum (n = 36), bone/skin (n = 6), lymph nodes (n = 34) and liver (n = 19) were 285, 209, 609 and 426 days, respectively. Prior receipt of S-1 adjuvant chemotherapy as well as absence of a measurable lesion and presence of multiple metastatic sites contributed to the poor prognosis following tumor recurrence. These prognostic factors identified in this study might become useful factors of stratification for future clinical trial design in patients with recurrent gastric cancer.

With respect to the efficacy of first-line chemotherapy given at the time of relapse, patients who had received S-1 adjuvant chemotherapy showed a significantly lower RR than those receiving no adjuvant treatment: 6.7 versus 42.9% (p = 0.0007) as shown in table 3. Likewise, in patients with recurrent breast cancer, adjuvant chemotherapy was demonstrated to be a significant factor in predicting a poor response to first-line chemotherapy after recurrence [21]. As for the choice of first-line regimen given at the time of relapse, about two thirds of patients in cohort A received non-S-1-based therapy after adjuvant S-1. Although 1 retrospective study reported the invalidity of S-1-based chemotherapy as first-line treatment for recurrent disease after adjuvant S-1 in terms of a significantly lower RR, DCR as well as shorter progression-free survival compared to non-S-1-based chemotherapy [22], it still remains a problem to be clarified prospectively whether patients failing S-1 adjuvant chemotherapy should subsequently be treated with non-S-1-based regimens. In fact, in cohort A, patients treated with non-S-1-based chemotherapy showed an MST of 287 days with RR of 9.5% and DCR of 52.4%, while those with S-1-based regimens demonstrated an MST of 268 days with RR of 0% and DCR of 33.3%, with no significant difference among them. These findings suggest that patients who recurred following S-1 adjuvant chemotherapy must have extremely aggressive tumors refractory to any kind of further chemotherapy.

The poor outcome following relapse in patients who had received adjuvant S-1 might be speculatively interpreted as follows. While noncurative adjuvant chemotherapy might eradicate sensitive tumor cells, adjuvant S-1 could screen and select biologically more aggressive cellular clones with intrinsic resistance to cytotoxic agents that progress more quickly once recurrence is identified, or could induce acquired cellular resistance to further chemotherapy, like anthracyclines which induce the development of multidrug resistance [23]. In either case, the tumor mass would be constituted mainly of resistant cells at the time of relapse or, as a consequence, a poor response to first-line chemotherapy and a shorter OS would be expected following recurrence. In a recent report [24], adjuvant S-1, compared to surgery alone, was shown to deteriorate recurrence-free survival as well as OS after curative gastrectomy when confined to patients with high intratumoral mRNA expression of thymidylate synthase (TS). Although high TS expression is well correlated with resistance to 5-FU [25] derived from S-1, these findings suggest that biologically more aggressive cancer cells could be induced by the S-1 administration in a tumor with high TS expression.

Irrespective of types of regimens, adjuvant chemotherapy was reported to be significantly associated with a low probability of response to first-line chemotherapy and shorter survival following recurrence in patients with recurrent breast cancer [21]. However, in the present study, adjuvant treatment with 5-FU agents other than S-1 showed modest effects on OS and RR compared to adjuvant S-1, though adjuvant S-1 adversely affected OS and RR in recurrent gastric cancer patients, as shown in figure 1 and table 3. It is not clear whether this difference in adverse effect between S-1 and other 5-FU agents depends on the ability in inducing chemoresistant cells of the respective agent.

DFI was not significantly prognostic of survival following recurrence on either univariate or multivariate analysis in this study, as shown in table 4. There have been some controversies about the effect of DFI on OS after recurrence. Patients recurred with longer DFI had superior survival to those with shorter DFI in recurrent colon cancer [20]. On the contrary, the MST of metastatic patients pretreated with adjuvant chemotherapy was independent of DFI in recurrent breast cancer [21]. In this study, the numbers of patients with a DFI less than 1 year, from 1 to 2 years, from 2 to 3 years and more than 3 years were 43, 29, 9 and 8, respectively. It remains possible for DFI to become a prognostic factor if the number of patients with a long DFI increases.

Of note, the MST of 287 days following recurrence in patients initially treated with adjuvant S-1 after curative gastrectomy was similar to that of 7 months yielded by the subsequent chemotherapy to S-1 in advanced/recurrent gastric cancer [12, 14]. No matter who received the first-line chemotherapy of S-1 as an adjuvant one or not, the OS after the usage of S-1 might be the same in patients who had recurrent tumor left after S-1 administration.

Although we believe that this is the first report demonstrating that patients initially treated with S-1 adjuvant chemotherapy had significantly inferior survival following recurrence and poorer response to first-line chemotherapy, compared with those without any adjuvant treatment after curative gastrectomy, it should be noted that the present study is a retrospective small-sized analysis performed at a single center. The results shown here warrant further study to elucidate the effect of S-1 adjuvant chemotherapy in patients with recurrent gastric cancer and to investigate an optimal regimen for patients relapsed after adjuvant S-1, though a prospective randomized study seems infeasible because adjuvant S-1 has become the standard treatment for stage II-III gastric cancer patients in Japan.


## Acknowledgement

We are grateful to Professor J. Patrick Barron, Tokyo Medical University, for the linguistic revision.


## References


1 Hermans J, Bonenkamp JJ, Boon MC, Bunt AMG, Ohyama S, Sasako M, Van de Velde CJH: Adjuvant therapy after curative resection for gastric cancer: meta-analysis of randomized trials. J Clin Oncol 1993;11:1441–1447.

2 Pignon J, Decreux M, Rougier P: Meta-analysis of adjuvant chemotherapy in gastric cancer: a critical reappraisal. J Clin Oncol 1994; 12:877–878.

3 Earle CC, Maroun JA: Adjuvant chemotherapy after curative resection for gastric cancer in non-Asian patients: revisiting a meta-analysis of randomised trials. Eur J Cancer 1999;35:1059–1064.

4 Mari E, Floriani I, Tinazzi A, Buda A, Belfiglio M, Valentini M, Cascinu S, Barni S, Labianca R, Torri V: Efficacy of adjuvant chemotherapy after curative resection for gastric cancer: a meta-analysis of published randomised trials. Ann Oncol 2000;11:837–843.

5 Janunger K, Hafstrom L, Nygren P, Glimelius B: A systematic overview of chemotherapy effects in gastric cancer. Acta Oncol 2001;40:309–326.

6 Panzini I, Gianni L, Fattori P, Tassinari D, Imola M, Fabbri P, Arcangeli V, Drudi G, Canuti D, Fochessati F, Ravaioli A: Adjuvant chemotherapy in gastric cancer: a meta-analysis of randomized trials and a comparison with previous meta-analyses. Tumori 2002;88:21–27.

7 Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, Haller DG, Ajani JA, Gunderson LL, Jessup JM, Martenson JA: Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 2001;345: 725–730.

8 Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, Scarffe JH, Lofts FJ, Falk SJ, Iveson TJ, Smith DB, Langley RE, Verma M, Weeden S, Chua YJ, MAGIC Trial Participants: Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006;355:11–20.

9 Sakuramoto S, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, Furukawa H, Nakajima T, Ohashi Y, Imamura H, Higashino M, Yamamura Y, Kurita A, Arai K, for the ACTS-GC Group: Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med 2007; 357:1810–1820.

10 Japanese Gastric Cancer Association: Japanese Classification of Gastric Carcinoma – 2nd English Edition. Gastric Cancer 1998;1: 10–24.

11 Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG: New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 2000;92:205–216.

12 Boku N, Yamamoto S, Shirao K, Doi T, Sawaki A, Koizumi W, Saito H, Yamaguchi K, Kimura A, Ohtsu A: Randomized phase III study of 5-fluorouracil (5-FU) alone versus combination of irinotecan and cisplatin (CP) versus S-1 alone in advanced gastric cancer. (JCOG 9912). J Clin Oncol 2007;25:LBA4513.

13 Shirasaka T, Shimamoto Y, Ohshimo H, Yamaguchi M, Kato T, Yonekura K, Fukushima M: Development of a novel form of an oral 5-fluorouracil derivative (S-1) directed to the potentiation of the tumor selective cytotoxicity of 5-fluorouracil by two biochemical modulators. Anti-Cancer Drug 1996;7: 548–557.

14 Koizumi W, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, Miyashita K, Nishizaki T, Kobayashi O, Takiyama W, Toh Y, Nagaie T, Takagi S, Yamamura Y, Yanaoka K, Orita H, Takeuchi M: S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol 2008;9:215–221.

15 Uedo N, Narahara H, Ishihara R, Takiuchi H, Goto M, Fujitani K, Hirao M, Tsujinaka T, Imano M, Furukawa H, Tsukuma H, Taguchi T: Phase II study of a combination of irinotecan and S-1 in patients with advanced gastric cancer (OGSG0002). Oncology 2007; 73:65–71.
16 Narahara H, Fujitani K, Takiuchi H, Sugimoto N, Inoue K, Uedo N, Tsukuma H, Tsujinaka T, Furukawa H, Taguchi T: Phase II study of a combination of S-1 and paclitaxel in patients with unresectable or metastatic gastric cancer. Oncology 2008;74:37–41.
17 Kodera Y, Ito S, Mochizuki Y, Fujitake S, Koshikawa K, Kanyama Y, Matsui T, Kojima H, Takase T, Ohashi N, Fujiwara M, Sakamoto J, Nakao A: A phase II study of weekly paclitaxel as second-line chemotherapy for advanced gastric cancer (CCOG0302 study). Anticancer Res 2007;27:2667–2672.
18 Futatsuki K, Wakui A, Nakao I, Sakata Y, Kambe M, Shimada Y, Yoshino M, Taguchi T, Ogawa N: Late phase II study of irinotecan hydrochloride (CPT-11) in advanced gastric cancer. Jpn J Cancer Chemother 1994;21: 1033–1038.
19 Koizumi W, Kurihara M, Satoh A, Takiuchi H, Tanabe S, Shimada K, Iwasaki R, Saigenji K: Phase I/II study of bi-weekly irinotecan plus cisplatin in the treatment of advanced gastric cancer. Anticancer Res 2005;25: 1257–1262.
20 O'Connell MJ, Campbell ME, Goldberg RM, Grothey A, Seitz JF, Benedetti JK, André T, Haller DG, Sargent DJ: Survival following recurrence in stage II and III colon cancer: findings from the ACCENT data set. J Clin Oncol 2008;26:2336–2341.
21 Venturini M, Bruzzi P, Del Mastro L, Garrone O, Bertelli G, Guelfi M, Pastorino S, Rosso R, Sertoli MR: Effect of adjuvant chemotherapy with or without anthracyclines on the activity and efficacy of first-line cyclophosphamide, epidoxorubicin, and fluorouracil in patients with metastatic breast cancer. J Clin Oncol 1996;14:764–773.
22 Shitara K, Muro K, Ura T, Takahari D, Yokota T, Sawaki A, Kawai H, Ito S, Yamamura Y: Chemotherapy for gastric cancer that recurs after adjuvant chemotherapy with S-1. Jpn J Clin Oncol 2008;38:786–789.
23 Eskiocak U, Erī OD, Kars MD, Biçer A, Gunduz U: Effect of doxorubicin on telomerase activity and apoptotic gene expression in doxorubicin-resistant and -sensitive MCF-7 cells. Chemotherapy 2008;54:209–216.
24 Ishido K, Azuma M, Koizumi W, Takeuchi A, Sakuramoto S, Watanabe M, Okayasu I: Evaluation of prognostic factors for the response to S-1 in patients with stage II or III advanced gastric cancer who underwent gastrectomy. Pharmacogenet Genomics 2009; 19:955–964.
25 Yasumatsu R, Nakashima T, Uryu H, Ayada T, Wakasaki T, Kogo R, Masuda M, Fukushima M, Komune S: Correlations between thymidylate synthase expression and chemosensitivity to 5-fluorouracil, cell proliferation and clinical outcome in head and neck squamous cell carcinoma. Chemotherapy 2009;55:36–41.

特集

抗癌剤腹腔内投与療法の現状

# 抗癌剤単回腹腔内投与＋逐次複数回全身投与療法の腹膜播種を伴う胃癌症例に対する効果

今野元博[*1,2]　安田卓司[*1]　平井紀彦[*1]　新海政幸[*1]
彭　英峰[*1]　安田　篤[*1]　白石　治[*1]　武本智樹[*1]
西山厚子[*1]　岩間　密[*1]　中森康浩[*1]　今本治彦[*1]
伊藤龍生[*3]　佐藤隆夫[*3]　奥野清隆[*1,2]　塩崎　均[*1]
大柳治正[*1]

**Single Course of Intraperitoneal Chemotherapy Followed by Multiple Course of Systemic Chemotherapy for Gastric Cancer Patients with Peritoneal Dissemination**: Imano M[*1,2], Yasuda T[*1], Hirai N[*1], Sinkai M[*1], Peng YF[*1], Yasuda A[*1], Shiraishi O[*1], Takemoto T[*1], Nishiyama A[*1], Iwama M[*1], Nakamori Y[*1], Imamoto H[*1], Itoh T[*3], Satou T[*3], Okuno K[*1,2], Shiozaki H[*1] and Ohyanagi H[*1] ([*1]Department of Surgery, [*2]Department of Ambulatory Treatment Center, [*3]Department of Pathology, Kinki University School of Medicine)

The prognosis of gastric cancer complicated by peritoneal dissemination is very poor and treatment for peritoneal dissemination is very difficult. Conventionally, intraabdominal chemotherapy with CDDP and MMC has been administered. However, it is not very effective and not generally available at present. Recently, treatment of peritoneal dissemination with S-1 and Paclitaxel it may be useful to combine treatment of peritoneal dissemination using these drugs with systemic treatment for gastric cancer. Therefore, we administered a single course of intraperitoneal chemotherapy followed by multiple courses of systemic chemotherapy for gastric cancer patients with peritoneal dissemination. In this trial of intraperitoneal chemotherapy followed by systemic chemotherapy with S-1 and Paclitaxel as the initial treatment for gastric cancer patients with peritoneal dissemination, we demonstrated the usefulness of this regimen with regard to both anticancer effect and toxicity.

**Key words**: Gastric cancer, Peritoneal dissemination, Intraperitoneal chemotherapy, Systemic chemotherapy
*Jpn J Cancer Clin* **54**(5): 329～336, 2008

## はじめに

腹膜播種を伴う胃癌患者の予後はきわめて不良で，従来は末期癌の状態であるとの認識が一般的であった．現行の第13版胃癌取り扱い規約では腹膜播種が成立する前段階と考えられている腹腔内に癌細胞が散布された状態（腹腔細胞診陽性）ですらStage Ⅳと位置づけられている[1]．しかし腹腔を，諸臓器を取り囲む局所の1つとして捉えた場合，局所療法として腹腔内化学療法が有効である可能性が示唆される．また，近年上市された新規抗癌剤を有効に使用することより，これらの病態に対して積極的な治療が行える可能性が表れてきた．本稿では抗癌剤単回腹腔内投与＋逐次複数回全身投与療法の理論的背景，ならびにわれわれの施行している，腹膜播種陽性症例に対する簡便かつ外来通院で治療継続が可能なpaclitaxel

*1 近畿大学医学部外科
*2 近畿大学医学部附属病院通院治療センター
*3 近畿大学医学部病理

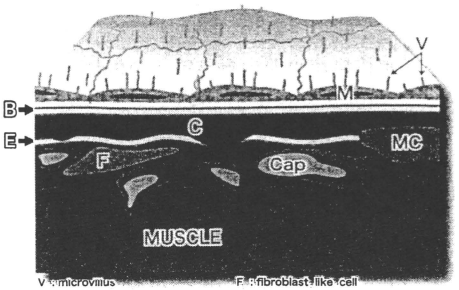
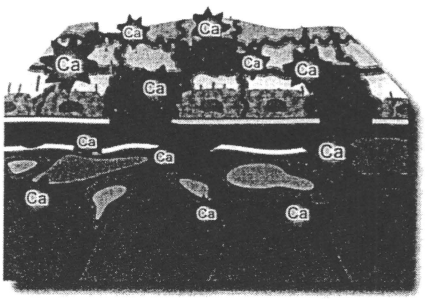



図1




Ca：Cancer cell
その他は図1と同一

図2

腹腔内投与と逐次S-1＋Weekly paclitaxel併用療法の現在までの治療成績について述べる．

## 1. 腹腔内単回化学療法と逐次複数回全身化学療法を組み合わせた腹膜播種に対する治療戦略（Hybrid Chemotherapy）

正常状態では腹膜は一層の扁平な中皮細胞と，筋層までの間に存在する豊富な脈管系を持つsub-methotelial layerからなる（図1）．癌細胞が漿膜を超えて浸潤した場合，もしくは脈管系を介して腹腔内に遊離するとほぼ同時期に，扁平な中皮細胞は立方化し細胞間に間隙を生じる，いわゆる反応性中皮細胞と呼ばれる形態に変化する．また，それに伴いsub-methotelial layerの肥厚が生じる．癌細胞はこの中皮細胞の間隙，もしくは何らかの理由で中皮細胞が剥離し基底膜の露出した腹膜に接着し，それを足がかりにsub-methotelial layerに浸潤し増殖する（図2）[2]．つまり癌性

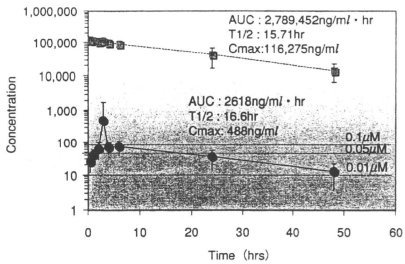



**図3　Paclitaxel腹腔内投与時の腹水中濃度および血漿中濃度の推移**

腹膜炎を治療するためには①腹腔内に遊離する癌細胞，②中皮細胞近傍に存在する癌細胞，③submethotelial layer深層に存在する癌細胞，この3つの領域に存在する癌細胞を標的としなければならない．

従来，癌性腹膜炎に対してcisplatin，mitomycin等の薬剤を用いた腹腔内投与療法が盛んに行われていた．cisplatinは腹膜クリアランスが比較的良好で，容易に血中に移行するためsystemicな有害事象を生じやすいという欠点がある．また薬剤が腹腔内の癒着を惹起するため，複数回の腹腔内投与を行うと均一な薬剤分布を得ることが困難になる．したがって，その治療成績を併せて考えると一般化されているとは言い難い[3]．

新規抗癌剤であるpaclitaxelはTaxus brevifolia（イチイ科）の樹皮粗抽出物から単離されたタキソイド系抗癌剤であり，tublineの重合を促進し安定な微小管を形成するとともにその脱重合を抑制することにより抗腫瘍効果を発揮する薬剤である[4]．胃癌に対する国内後期第Ⅱ相試験の結果，奏効率28％であった[5]．また分子量が853.92と大きいことや，脂溶性であることから腹腔内に投与した場合，腹腔内貯留時間が長い特性を示す[6]．腹腔内投与後24時間での血中ならびに腹水中の時間曲線下面積（AUC）の比は症例によってばらつきがあるものの，550～2,000と報告されている[7]．また，われわれの腹腔内投与後48時間後までのデーターでも，血清濃度と腹腔内濃度のAUCは平均で約1,000倍の差が認められた（図3）．またこの薬剤の特徴として，静脈内に投与した後の腹水への良好な移行性があげられ，血中濃度に対して1.4倍であると報告されている[8]．

同様に新規抗癌剤の一種であるS-1は経口5-fluorouracil（5-FU）系抗癌剤で5-FUのプロドラッグであるtegafulにgimeracilおよびoteracil potassiumの2つのモジュレーターをモル比1：0.4：1で配合した製剤である．TS-1単剤の4週投与2週休薬法による切除不能進行再発胃癌に対する後期第Ⅱ相臨床試験の結果では，奏効率44％（19/43），MST（median survival time）は207日と良好な結果を得ている[9]．またpaclitaxelと同様に，経口薬剤でありながら腹水中への移行が良好で，血漿中の濃度とほぼ同等であると報告されている[10]．

われわれはこの2種類の薬剤を効率的に使用する癌性腹膜炎の治療を考案した．つまり上記の腹腔内に遊離する癌細胞ならびに中皮細胞近傍に存在する癌細胞に対しては，paclitaxelを腹腔内に直接投与することにより，これらの標的に静脈投与では到底得ることのできない濃度の抗癌剤を直接接触させ，その効果を期待する（図4）．腹腔内に投与されたpaclitaxelは腹膜クリアランスが不良なため血中に移行することが少ないことから，systemicな有害事象を引き起こす確立は低い．しかし腹腔内に投与されたpaclitaxelの腹膜