**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.


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CASE REPORT

# Complete response to preoperative chemoradiotherapy in highly advanced gastric adenocarcinoma

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## Abstract

This report presents a case of highly advanced gastric cancer that achieved a histologically complete response (CR) to preoperative chemoradiotherapy with S-1 plus low-dose Cisplatin. A 60-year-old male patient underwent FDG positron emission tomography (PET) during a routine health examination. The patient was found to have swollen paraaortic lymph nodes. Shortly thereafter, he was diagnosed with gastric carcinoma with a type 2 tumor in the antrum with paraaortic lymph node metastases based on FDG-PET, endoscopic examination and abdominal computed tomography. After the completion of chemoradiation therapy (CRT), the tumor and the paraaortic lymph node metastases disappeared. The patient underwent surgery 5 wk after the completion of CRT, including a subtotal gastrectomy with Roux-en-Y reconstruction, D3 lymph node dissection and a left adrenalectomy. No cancer cells were detected in the resected specimen either in the primary lesion or lymph nodes, thus confirming a pathologically CR to CRT (CR grade 3). The patient has been stable and well without any evidence of recurrence for 48 mo after surgery. Such a preoperative CRT regimen might therefore be very effective for treatment of some advanced gastric cancers.



**Key words:** Complete response; Gastric cancer; Cisplatin; Chemoradiation; Neoadjuvant therapy

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## INTRODUCTION

Surgical therapy and endoscopic resection is the primary treatment for gastric carcinoma. However, for patients with stage IV advanced gastric cancer the prognosis is unfavorable even if macroscopically curative resection is performed.

Several new perioperative adjunctive approaches (neoadjuvant and/or adjuvant) for highly advanced gastric cancer have been explored[1-4]. Although a high incidence of partial response by chemotherapy with S-1 plus Cisplatin has been reported, a pathologically complete response (CR) is seldom observed with this combination. Therefore, chemoradiation therapy (CRT) has attracted considerable

attention as a breakthrough for treating cases of highly advanced gastric cancer.

This report presents the case of a patient initially diagnosed with an unresectable advanced gastric cancer who was successfully treated by preoperative chemoradiotherapy with S-1 plus low-dose Cisplatin. The patient achieved a histologically CR that continued to a long-term survival of more than four years without any recurrence.

## CASE REPORT

A 60-year-old male patient was found to have swollen paraaortic lymph nodes by FDG positron emission tomography (PET) (Figure 1A) during a routine health examination. The patient had no complaints and no palpable mass was found by an abdominal physical examination. The serum carcinoembryonic antigen and carbohydrate antigen (CA) 19-9 levels were negative, 2.0 mg/mL and 9 U/mL respectively. The serum sIL-2R level was 669 U/mL which was slightly increased over normal levels. The blood chemistry findings were all normal and the hemoglobin level was 15.9 g/dL. The chest X-ray was also normal. Gastrointestinal fiberscopy showed a type 2 gastric carcinoma in the antrum (Figure 2A). An endoscopic biopsy revealed an intestinal type adenocarcinoma (moderately differentiated tubular adenocarcinoma; Figure 2B). Previously, the patient had undergone a gastrointestinal endoscopic examination almost every year. Unfortunately, he did not have an endoscopic examination in the year prior to the FDG-PET since there had been no symptoms such as stomach pain.

Abdominal computed tomography (CT) also revealed lymph node metastases in the paraaortic region (Figure 3A and B). Therefore, this case was diagnosed to have stage IV advanced gastric carcinoma using the Japanese classification of gastric carcinoma (cT2, cN3, cH0, cP0, cM0). Stage IV gastric cancer was also indicated by the UICC TNM classification because of the paraaortic lymph node metastasis.

Preoperative CRT was administered since the tumor was apparently too advanced to be curatively resected. A 10 MV X-ray was used. The daily fractional dose of radiation therapy was 1.8 or 2 Gy, administered 5 d a week. The radiation treatment was delivered through the anterior and orthogonal lateral portals with 45-degree wedges. The radiation fields included the body and antrum of the stomach, the perigastric lymph nodes and the lower paraaortic lymph nodes. Concurrent chemotherapy was combined with radiation therapy of 40 Gy over 22 fractions for 5 wk. S-1 (1 M tegafur-0.4 M gimestat-1 M otastat potassium) was administered orally at a dose of 120 mg/d on days 1-14 and at a dose of 80 mg/d on days 21-34 and 17 doses of CDDP (7 mg/d) were infused for 1 h prior to radiation therapy. The dose of S-1 in the latter half was reduced to 80 mg/d due to adverse reactions (grade 2 leukocytopenia and grade 2 fatigue). The tumor and the paraaortic lymph node metastases completely disappeared at the completion of CRT (Figure 3C and D) thus leaving a tiny area of erosion on the mucosa of the antrum (Figure 2C). Grade 3 leukocytopenia and grade 2 thrombocytopenia were the only adverse effects observed after CRT.

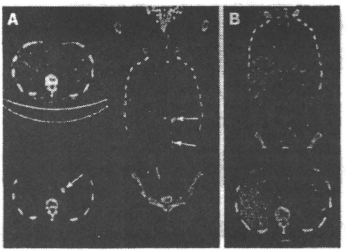


**Figure 1 F-18 2-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) computed tomography CT findings.** A: FDG-PET CT showing lymph nodes metastases in the paraaortic region (arrows); B: After chemoradiation therapy (CRT), FDG-PET CT demonstrated a marked reduction of the lymph nodes.

Five weeks after the completion of CRT, the patient underwent surgery, including a subtotal gastrectomy with Roux-en-Y reconstruction, D3 lymph node dissection and a left adrenalectomy (Figure 4A and B). No cancer cells were detected in the resected specimens in the primary lesion (Figure 4C) or in the lymph nodes (Figure 4D), confirming a pathologically CR (CR grade 3).

The patient had no surgical complications and was discharged from the hospital 10 d after surgery. The patient received no adjuvant chemotherapy and is presently alive and well at 48 mo after surgery with no evidence of recurrence.

## DISCUSSION

Gastric cancer is one of the most frequent malignant tumors in the world. A gastric cancer screening program was introduced in the 1960s in Japan as a public health service. Since that time, the proportion of early stage gastric cancer has been increasing. However, highly advanced gastric cancer patients such as the current patient are still frequently diagnosed. The patient described in this case report was initially found to have swollen paraaortic lymph nodes by FDG-PET during a routine health examination. He subsequently underwent gastrointestinal fiberscopy which revealed a type 2 tumor in the antrum. Thereafter, an endoscopic biopsy revealed an intestinal type adenocarcinoma. FDG-PET is usually not used to detect or stage gastric cancer. Chen *et al*[5] reported that FDG-PET demonstrated an increased uptake in 64 of 68 patients (sensitivity 94%) and also improved the preoperative TNM staging of adenocarcinoma. FDG-PET was therefore found to be very useful in this case. In addition, it may also be complementary to CT scans for the preoperative staging of gastric cancer.

Because this case was diagnosed to have stage IV ga-

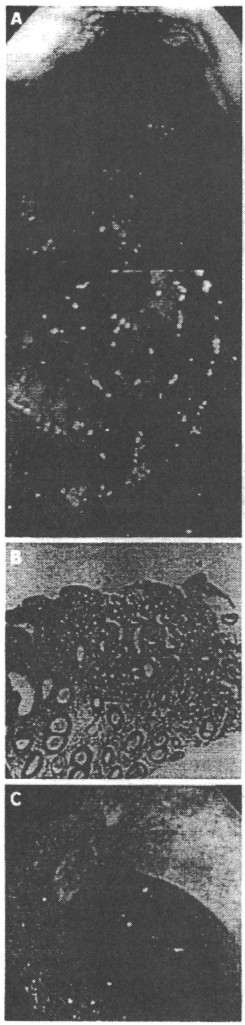


**Figure 2 Gastrointestinal fiberscopy (GIF) and preoperative biopsy findings.** A: GIF before CRT demonstrating advanced type 2 gastric cancer at the antrum; B: Microscopic finding of the biopsy specimen obtained from the tumor, showing intestinal type adenocarcinoma (moderately differentiated tubular adenocarcinoma, Hematoxylin-Eosin 40X); C: GIF after CRT demonstrating the tiny erosion on the mucosa of antrum.

stric cancer using the Japanese classification of gastric carcinoma due to paraaortic lymph node metastases, the prognosis was unfavorable even if an R0 resection (complete local-regional tumor removal with negative resection margins) could be performed. A successful preoperative therapeutic strategy consisting of either chemotherapy or chemoradiotherapy may improve R0 resection and reduce recurrence, although the efficacy of neoadjuvant therapy for advanced gastric cancer is still controversial[6,7]. Adjuvant therapy may also be useful. The MAGIC trial demonstrated that pre and postoperative ECF regimens (a combination of Epirubicin, CDDP and a continuous infusion of 5-FU) decreased the tumor size and stage and significantly improved the rates of progression-free survival[8].

S-1 is an effective anticancer therapy. Even if given alone, the response rate is approximately 40%-50%[9,10]. Combination chemotherapy with S-1 and CDDP has demonstrated a favorable antitumor activity[11-14]. There are some case reports with a CR of gastric cancer by S-1 monotherapy[15,16] and chemotherapy with S-1 plus low-dose CDDP[17]. Preoperative CRT using S-1 and low-dose CDDP (4 mg/m$^2$ per day) was administered to the current patient.

Ajani *et al*[18] reported the overall survival of patients who achieved a pathologically CR (pathCR) to be significantly longer than that of patients who did not have a pathCR. The frequency of pathCR by preoperative chemotherapy is much less than that by preoperative CRT which was the reasoning for administering preoperative CRT in the current case. A phase II multi-institutional trial by the Radiation Therapy Oncology Group (RTOG 99-04) of pre-operative chemoradiation for localized gastric adenocarcinoma demonstrated the pathologic CR and R0 resection rates to be 26% and 77% respectively[19].

Fortunately, preoperative CRT was very effective for this patient and the paraaortic lymph node metastases disappeared after the completion of CRT, confirmed both by FDG-PET and CT scans. A complete pathologic response of advanced gastric adenocarcinoma has been achieved with several regimens[20,21]. A curative resection could not have been performed if the preoperative CRT had not been effective in this case. Radiation was very effective in this case. There are very few pathCR case reports of highly advanced gastric cancer with neoadjuvant CRT which describe a large radiation field including the paraaortic area. Advances in conformal radiation and chemotherapy-based treatment planning now allow for the treatment of such a large radiation field and for it to be combined with chemotherapy.

Neoadjuvant approaches are very attractive because the pathologic response can be precisely assessed in the treated tumor. Pre-operative CRT does have potential risks. The RTOG 99-04 reported Grade 4 toxicity in 21% of all patients. Although preoperative CRT has been used to treat patients with potentially resectable localized gastric adenocarcinomas in some countries, preoperative CRT is usually applied for unresectable cases in Japan. Preoperative CRT might be useful as a standard procedure for advanced gastric cancer after the completion of the phase III trial.

The radiation doses of 31 to 50 Gy have been applied

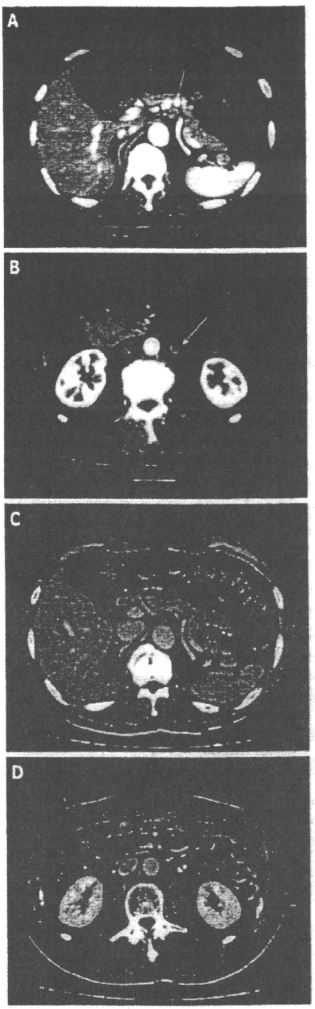


**Figure 3 Abdominal CT scan findings.** A: CT scan showing lymph node metastasis in the lymph nodes around the celiac artery (arrow); B: Abdominal CT showing lymph node metastasis in the paraaortic region (arrow); C, D: After CRT, abdominal CT demonstrated a remarkable reduction of lymph node size.

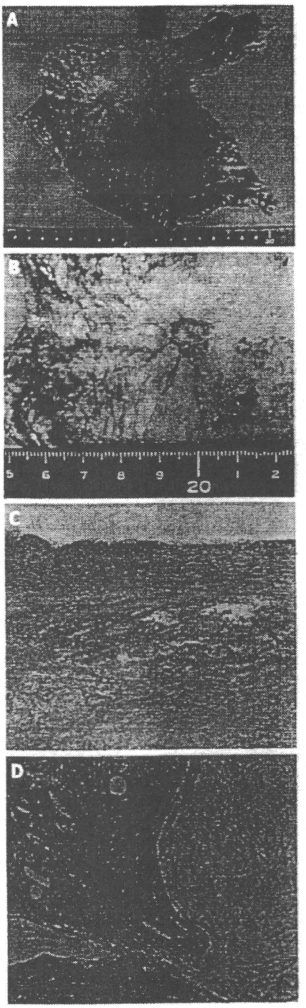


**Figure 4 Resected specimen and histopathological findings.** A, B: Macroscopic appearance of the surgically resected stomach. An ulcerative lesion was identified on the lesser curvature of the antrum. No tumor cells were observed in either the primary lesion (C, HE stain, 40×) or the dissected lymph nodes (D, HE stain, 40×), thus confirming a grade 3 effect (pathological complete response, pCR) for the treatment regimen.

for preoperative treatment[7]. The radiation dose was 40 Gy in the present case and it yielded a pathologic CR.

Although the role of chemotherapy as an adjuvant treatment remains controversial, several randomized trials have shown the advantages of adjuvant chemotherapy. No adjuvant chemotherapy was administered in the current case because no cancer cells were detected in any of the resected specimens.

This report presented the case of a successfully treated patient who had highly advanced gastric carcinoma with paraaortic lymph node metastases.

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

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**Abstract**

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


*Keywords:* Gastric cancer; Chemotherapy; Surgery; Phase II

## Introduction

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

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

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

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

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

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

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

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

## Patients and methods

### *Eligibility criteria*

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

### *Preoperative chemotherapy*

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

*Surgery*

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

*Treatment defined by the protocol*

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

*Endpoints*

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

*Evaluation*

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

*Statistical hypothesis*

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

## Results

*Patients*

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

*Preoperative chemotherapy and toxicities*

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

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

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

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

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

*Clinical response*

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

*Surgery*

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

*Surgical morbidity and mortality*

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

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

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

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

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

[a] Three missing cases were exploratory laparotomy.

*Pathological response*

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

*Overall survival*

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

## Discussion

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

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

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

Table 5
Pathological results.

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

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

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

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

*Surgical mortality*

No operative mortality was observed in the study, although 39 of the 49 patients underwent D2 or D3 surgery after preoperative chemotherapy. In the Japan Clinical Oncology Group (JCOG) 9501 phase III trial that compared D2 and D3 resections, mortality rate was reported to be 0.8% in both arms.[12] Thus, our results suggested that mortality of D2 or D3 was not increased by preoperative chemotherapy with S-1 plus cisplatin. In the retrospective study evaluating the feasibility and safety of preoperative chemotherapy of S-1 plus cisplatin followed by D2 dissection, no operative mortality was reported.[20,21] In the MAGIC phase III trial comparing surgery alone versus pre- and postoperative chemotherapy combined with surgery for resectable gastric cancer, operative mortality was 5.6% in the chemotherapy group and 5.9% in the surgery group, suggesting that mortality did not increase by preoperative chemotherapy (with an ECF regimen).[19] However, in that trial, most patients underwent less than D2 surgery. On the other hand, in JCOG 0001 trial evaluating the efficacy and safety of preoperative chemotherapy of CPT-11 plus cisplatin followed by D3 surgery, operative mortality was observed in 2.0%.[13] Thus, operative mortality may depend on the toxicity of the preoperative chemotherapy and the extent of the lymph node dissection.

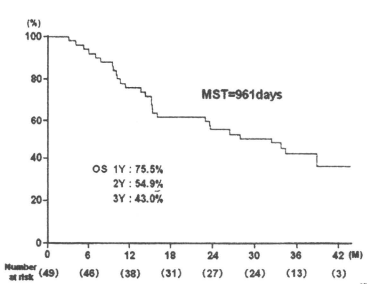


Figure 1. Overall survival ($n = 49$). Median survival time was 31.5 months. Overall survival was 75.5% at 1 year, 54.9% at 2 years, and 43.0% at 3 years.

*Pancreas-related surgical morbidity*

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

*Overall surgical morbidity*

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

*Chemotherapy-related toxicities*

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

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

*Response to the chemotherapy*

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

*Survival*

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

*Conclusion*

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

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**Conflict of interest**

No authors have any conflict of interest.



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特集 ……Stage Ⅳ胃癌における外科治療の有用性……

# 腹腔洗浄細胞診陽性例に対する肉眼的治癒切除の意義

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**Significance of R1 Resection in Patients with Positive Peritoneal Cytology**: Terashima M*1, Bando E*1, Tokunaga M*1, Tanizawa Y*1, Kawamura T*1, Kondo J*1, Sugisawa N*1, Taki Y*1, Ohsima N*1, Motegi Y*1, Miki Y*1, Yamakawa Y*1, Makuuchi M*1, Kinugasa Y*2, Kanemoto H*2, Uesaka K*2, Yasui H*3 and Boku N*4 (*1Division of Gastric Surgery, *2Division of Gastrointestinal Surgery, *3Division of Medical Oncology, Shizuoka Cancer Center, *4Department of Internal Medicine, St. Marianna University, School of Medicine Hospital)

Positive peritoneal cytology (CY1) is regarded as M1 disease and classified into stage Ⅳ. However, it is still controversial whether the prognosis in patients with CY1 is same as hepatic metastasis or peritoneal seeding or not. In order to determine the optimal treatment strategy for patients with CY1, we retrospectively evaluated the results of patients with CY1. A total of 123 patients with M1 (CY1) without other non-curative factors and underwent gastrectomy were included in this study. There was a significant difference of survival betweenR1 and R2 resection. In the multivariate analysis in patients underwent R1 resection, N-factor, D2 lymph node dissection, and adjuvant chemotherapy with S-1 were selected as independent prognostic factor. The median survival time and 5-year survival rate in patients underwent R1 resection with D2 lymphadenectomy and adjuvant S-1 treatment were 42 months and 46%, respectively. In patients with positive peritoneal cytology without other non-curative factors, D2 lymph node dissection to achieve R1 resection and adjuvant chemotherapy using S-1 is recommended.

**Key words**: Gastric cancer, Peritoneal cytology, D2 lymph node dissection, R1 resection, Adjuvant chemotherapy
*Jpn J Cancer Clin* **56**(4): 291～295, 2010

## はじめに

以前からわが国においては腹腔洗浄細胞診に関する研究が広く行われており，腹腔洗浄細胞診陽性例はきわめて予後が不良であることが報告されてきた[1,2]．これらの研究結果を受けて1999年に発行された胃癌取扱い規約第13版から腹腔細胞診（CY）が規定され，細胞診陽性（CY1）はすなわちStage Ⅳであり，肉眼的な根治切除が行われても根治度Cに分類される事になった[3]．最近改訂されたTNM分類第7版においても洗浄細胞診によるステージングが導入され，細胞診陽性は肝転移や腹膜転移と同様に遠隔転移（M1）に分類され，residual tumorにおいても肉眼的な根治切除が行われたとしてもR1（microscopic

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residual tumor）に分類される[4]．今回改訂された胃癌取扱い規約第14版[5]でも同様の分類が採用されている．しかし，CY1が他の遠隔転移と同様の予後を示すか否かについては疑問であり，特にわが国においてはS-1の開発以降[6,7] CY1であっても術後のS-1投与により長期生存する症例もしばしば経験する．これまで当施設においても他に非治癒因子の無いCY1症例に対しては可能な限り肉眼的治癒切除（R1）を行い，術後S-1を投与してきた．

そこで，今回CY1単独によるStage Ⅳ症例に対する至適な治療戦略を検索する目的で，これまでのR1切除症例の治療成績について検討した．

## 1 対象と方法

2002年10月から2009年6月までに当科で加療を行った胃癌2,299例中，他に非治癒因子が無く腹腔洗浄細胞診にてCY1と診断され，切除が施行された123例を対象とした．

これらの症例において，臨床病理学的因子，生存期間並びに多変量解析による予後因子の解析について検討した．

臨床病理学的因子に関しては胃癌取り扱い規約第13版に準じて記載したが，腫瘍の遺残（R）のみは同第14版[5]に準じた．

生存曲線はKaplan-Meier法にて作成し，生存期間の解析にはCoxの比例ハザードモデルを用いた．

## 2 結　果

### 1 CY1切除症例の臨床病理学的因子

CY1切除症例の臨床病理学的因子の検討（表1）では，一般の胃癌と比較して，女性の割合が比較的高く，当然の事ながらT3以深の症例が大多数を占めていた．93%の症例でリンパ節転移を伴っており，肉眼的には3型，4型の症例が3/4を占めており，組織学的には約2/3の症例が未分化型であった．

実際に行われた治療内容（表2）では，癌の進行度を反映してか胃全摘の症例が59%を占め，

表1　CY1切除症例の背景因子

| | | | |
|---|---|---|---|
| 年齢 | 65.8±10.6 | 組織型 | |
| 性別 | | 分化型 | 33 |
| 男性 | 78 | 未分化型 | 90 |
| 女性 | 45 | 肉眼型 | |
| 胃壁深達度 | | 0 | 2 |
| T1 | 1 | 1 | 4 |
| T2 | 22 | 2 | 23 |
| T3 | 88 | 3 | 65 |
| T4 | 12 | 4 | 28 |
| リンパ節転移程度 | | 5 | 1 |
| N0 | 9 | 腹腔洗浄細胞診 | |
| N1 | 35 | Class Ⅳ | 11 |
| N2 | 63 | Class Ⅴ | 112 |
| N3 | 16 | | |

表2　CY1切除症例に実施された治療内容

| | | |
|---|---|---|
| 切除術式 | 幽門側胃切除 | 46 |
| | 胃全摘 | 73 |
| | 膵頭十二指腸切除 | 4 |
| 郭清程度 | D1+α | 32 |
| | D1+β | 23 |
| | D2 | 66 |
| | D3 | 1 |
| 根治度（TNM） | R1 | 105 |
| | R2 | 18 |
| 術後S-1投与 | あり | 95 |
| | なし | 28 |

膵頭十二指腸切除も4例に施行されていた．リンパ節郭清に関しては，D2以上の郭清が実施された症例が約半数を占める一方，残りの半数の症例ではD1+αやβに留まっていた．その結果，根治度に関しては85%の症例でR1切除が可能であった．

### 2 CY1症例における根治度別の生存期間の検討

CY1症例における生存転帰の解析では，治癒切除の程度で最も大きな差が認められた（図1）．R1切除例の生存期間中央値（MST）は20.5月であったのに対し，R2切除例では11.0月と著明に短縮しており有意な差が認められた．R因子が最も重要な予後因子であり，R2切除例は少数例のみであったため以降予後因子の解析はR1切除

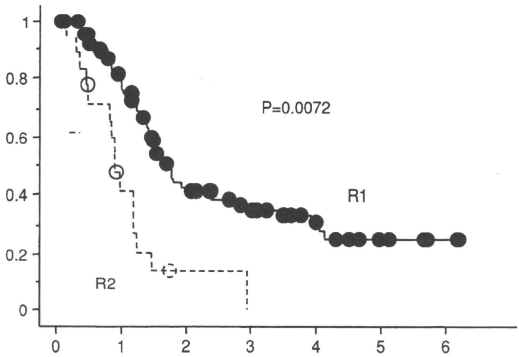


図1　CY1切除症例における根治度別の生存曲線

例に限って検討した．

**3）CY1, R1切除例における生存期間の検討**

表3にCY1でかつR1切除が可能であった症例における臨床病理学的因子と生存期間との関連について単変量解析，多変量解析の結果を示した．単変量解析の結果では，壁深達度，リンパ節転移程度では有意な差が認められず，リンパ節郭清程度（<D2 vs ≧D2），術後S-1投与の有無のみで有意な差が認められた（表3）．

一方，多変量解析の結果では，リンパ節転移程度，リンパ節郭清程度，術後S-1投与が有意な独立した予後因子として選択された．

**4）CY1, R1切除，>D2郭清，術後S-1投与症例の生存曲線**

上記の解析の結果で良好な予後を示すと思われる，>D2郭清が施行され，術後S-1が投与された症例の生存曲線に関して検討した（図2）．D2以上の郭清が施行されてかつ術後S-1が投与された症例のMSTは42月で，5年生存率は46%であった．

表3　CY1, R1切除例における臨床病理学的因子と生存期間との関連

| 臨床病理学的因子 | 単変量解析 | | 多変量解析 | |
|---|---|---|---|---|
| | HR | p値 | HR | p値 |
| 性別 | | | | |
| 男性 | 1.000 | | 1.000 | |
| 女性 | 0.906 | 0.7094 | 0.956 | 0.8726 |
| 壁深達度 | | | | |
| T1, T2 | 1.000 | | 1.000 | |
| T3, T4 | 1.471 | 0.2043 | 1.783 | 0.0877 |
| リンパ節転移 | | | | |
| N0, N1 | 1.000 | | 1.000 | |
| N2, N3 | 1.324 | 0.2938 | 1.919 | 0.0264 |
| 組織型 | | | | |
| 分化型 | 1.000 | | 1.000 | |
| 未分化型 | 1.063 | 0.8260 | 1.027 | 0.9283 |
| リンパ節郭清程度 | | | | |
| D1, D1+α, D1+β | 1.000 | | 1.000 | |
| D2, D3 | 0.572 | 0.0308 | 0.476 | 0.0059 |
| 術後S-1投与 | | | | |
| なし | 1.000 | | 1.000 | |
| あり | 0.498 | 0.0154 | 0.430 | 0.0102 |

## 3．考　察

これまでCY1症例はきわめて予後が不良であり，腹膜播種を有する症例と同程度の生存期間を示すと認識されてきた[1,2]．そのため，胃癌取り扱い規約においても第13版以降は，CY1すなわちStage Ⅳであり，仮に肉眼的に根治切除がなされても根治度Cに分類される事になった．したがって胃癌治療ガイドラインにおいても，化学療法，放射線治療，緩和手術，対症療法が日常診療として推奨されており，これはつい最近改訂さ

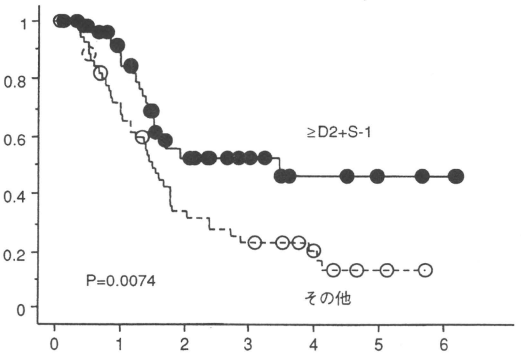


**図2　CY1, R1 切除例中≥ D2 郭清，術後 S-1 投与症例の生存曲線**

れた第3版でも同様の扱いである[8]．

しかし，その後わが国において開発されたS-1が胃癌に対して優れた抗腫瘍効果を示す事が確認され，進行再発胃癌[6]のみならず，Stage Ⅱ，Ⅲの根治切除例に対する補助化学療法においても有効性が証明されるようになった[7]．CY1症例に対して至適な補助療法は確立されていなかったため，当院ではS-1単独による化学療法（原則として1年間）が施行されていた．

CY1切除例の背景因子の解析では，これまで報告されてきた結果[1,2]と同様に，肉眼型が3型，4型の進行胃癌で，未分化型で漿膜浸潤陽性の腫瘍が大半を占めていた．

これらの症例における予後因子の解析では，リンパ節転移の程度とともに，リンパ節郭清程度，根治度，術後S-1投与が予後因子として選択された．つまり，CY1はStage Ⅳであり肉眼的治癒切除を行っても根治切除にはならないとは言え，その予後は他の遠隔転移を有する症例とは明らかに異なっており，可能な限り腫瘍遺残量の少ない手術を施行する事が重要と思われた．また，術後S-1を投与する事により有意に生存期間の延長が認められる事から，Stage Ⅱ，Ⅲの根治切除例と同様，CY1症例においても術後S-1投与の有効性が示唆された結果である．寺本ら[9]はCY1の予後予測性に関して検討し，他に非治癒因子の無いCY1症例は，他のStage Ⅳと同様に扱うべきではないと結論している．また，岩下ら[10]はCY1症例の予後因子に関して検討し，P0CY1の症例ではD2以上の郭清によりR1切除を目指し，術後化学療法を行う事により良好な予後が得られる可能性を示唆している．いずれも今回のわれわれの検討結果を支持するものである．

もちろん，今回の検討はretrospectiveな解析であるため，様々なbiasが生じていることは否めない．CY1と言っても全身状態が比較的良好で，腫瘍量が少ない症例に限ってD2以上の郭清がなされ，術後のS-1投与が実施されていた可能性も否定できない．CY1症例に対して至適な治療戦略が確立されていない現状では，curative intentで開腹手術に望んだ場合には可及的に肉眼的根治切除を目指して，その後S-1による化学療法を施行する事が推奨される．しかし，この治療法が最善であるという根拠は無い．中川ら[11]はCY1症例に対して術前化学療法を施行する事により78%の症例でCYの陰性化が得られる事を報告している．術前診断でCY1の高危険群に対しては審査腹腔鏡を施行し，CY1であれば術前化学療法を施行する事により治療成績の向上が得られる可能性もある．また，CY1症例は抗癌剤の腹腔内投与の良い適応である事も示唆されている[12]．このようにCY1単独でStage Ⅳに分類される症例に対しては，様々な治療法により治療

成績の向上が得られる可能性が残されている．今後，前向きの臨床試験により至適な治療戦略の確立が切望される．

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