Surgical findings and surgical pathology

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

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

Adverse events from chemotherapy

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

Surgical complications

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

Overall survival

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

Table 4 Surgical complications in the 49 operated patients

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

Values in parentheses are percentages.

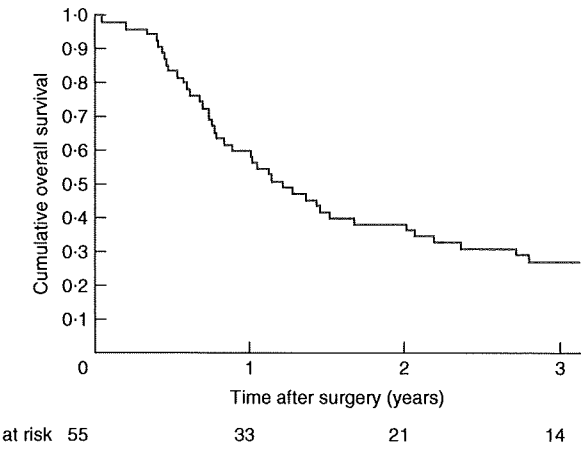

Fig. 4 Kaplan–Meier overall survival curve for the 55 eligible patients

Discussion

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

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

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

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

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

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

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A phase II study of radical surgery followed by postoperative chemotherapy with S-1 for gastric carcinoma with free cancer cells in the peritoneal cavity (CCOG0301 study)

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Abstract

Background: Patients with gastric cancer who have positive cytologic results for cancer cells in peritoneal washings (CY1) have poor outcomes, even in the absence of other distant metastases. A standard treatment for such patients remains to be established.
Methods: We conducted a phase II trial with the 2-year survival rate as the primary endpoint. Patients who had gastric cancer with CY1 status but no other residual disease received postoperative chemotherapy with S-1 (1 M tegafur–0.4 M gimestat–1 M otastat potassium) at a daily dose of 80 mg/m^2 for 4 weeks, followed by 2 weeks of rest. This cycle was continued until disease progression or intolerable adverse events. D2 dissection was the recommended surgical procedure; splenectomy could be omitted at the discretion of the surgeon. Accrual of 50 patients was planned, and a 2-year survival rate of more than 36% was needed to exceed the historical control.
Results: Forty-eight patients were enrolled, among whom 47 were assessable for survival and 46 for adverse reactions. Median overall survival was 705 days, and progression-free survival was 376 days. The 2-year survival rate was 47%. Median time to treatment failure was 288 days. Neutropenia was the commonest ≥grade 3 toxicity (6 patients), and anorexia was the most frequent ≥grade 2 non-hematologic toxicity (10 patients).
Conclusions: Gastrectomy followed by S-1 monotherapy resulted in survival that surpassed historical data and can serve as an active control treatment for future trials in patients who have gastric cancer with CY1 status in the Far East.

Keywords: Gastric cancer; S-1; Cytologic examination; Peritoneal carcinomatosis

Introduction

Despite the declining incidence in Western Europe[1] and the United States,[2] gastric carcinoma remains the second most common cause of cancer-related death worldwide, with over 600 000 deaths per year.[3] Peritoneal carcinomatosis is a major pattern of disease recurrence after D2 dissection, a standard procedure in the Far East that presumably improves locoregional control.[4,5] Similar problems could also develop in the United States if a strategy of D1 dissection followed by chemoradiation is found to achieve good local control.[6] Peritoneal metastasis is generally considered to arise from free cancer cells shed from the serosal surface of locally advanced gastric cancer. Such cells, if present, can be detected by cytologic examination of peritoneal washings,[7] a standard diagnostic procedure performed for accurate staging in all patients with advanced

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gastric cancer who undergo surgery in Japan. Positive cytologic results for cancer cells indicate a very high risk of peritoneal carcinomatosis. The Japanese Classification of Gastric Carcinoma classifies positive cytologic results as CY1 status. Patients with CY1 status are automatically considered to have Stage IV disease, and surgery is classified as curability C, i.e., noncurative resection.[8] The prognostic significance of positive cytologic results of peritoneal washings has also been acknowledged in Europe,[9] and more recently, in the United States.[10]

Currently, there is no standard treatment for patients found to have CY1 status after surgery. Surgeons in Japan encounter this situation rather frequently, because preoperative evaluation with the cytologic examination in addition to staging laparoscopy[11] remains an option, not a standard of care for the patients with locally advanced cancer. Hence, results of the cytologic examination are often obtained only after the surgery. Since gross peritoneal carcinomatosis indicates incurable disease, early treatment with anticancer drugs is usually recommended in addition to surgery for CY1 disease. S-1 (1 M tegafur–0.4 M gimestat–1 M otastat potassium) has had response rates of >40% in phase II trials[12,13] and good tolerability in patients with gastric cancer when given within 2–6 weeks after surgery.[14] A pivotal phase III trial conducted in Japan has shown that S-1 is effective in a postoperative adjuvant setting in patients with stages II and III gastric cancer.[15] These promising results have led to the increased use of S-1 for postoperative treatment in patients with CY1 disease. In the present study, patients who underwent R1 resection and had microscopic evidence of residual disease only in the form of free cancer cells in the abdominal cavity postoperatively received oral S-1. Our main objective was to evaluate the 2-year survival rate as compared with a historical control.

Patients and methods

Patient eligibility

Eligible patients had to meet all of the following criteria: (i) a confirmed diagnosis of gastric adenocarcinoma and an age of less than 80 years; (ii) gastrectomy with systemic lymphadenectomy, preferably with D2 dissection, performed; (iii) no distant metastasis with the exception of minimal peritoneal deposits that were completely resected; (iv) no prior treatment besides surgery; and (v) positive cytologic results for cancer cells on examination of peritoneal washings (CY1). Cytologic examination was performed as recommended by the Japanese Classification of Gastric Carcinoma,[8] i.e., 100 mL of saline was introduced into the pouch of Douglas, stirred gently, and aspirated. Direct washing of the serosa of the stomach or of the upper abdominal cavity was not performed. The specimens were examined by board-certified pathologists after conventional Papanicolaou and Giemsa staining. It was not mandatory to obtain the results of cytologic examinations during surgery. The interval from surgery to the start of therapy was not to exceed 6 weeks. Other eligibility criteria included a Cooperative Oncology Group performance status of 0–2, and adequate organ functions, defined as total neutrophil count $\geq 3000/mm^3$, platelet count $\geq 100\,000/mm^3$, hemoglobin ≥ 8.0 g/dL, serum creatinine within the normal range according to the criteria of the hospital where the test was performed, total serum bilirubin <1.5 mg/dL, and serum aspartate aminotransferase and alanine aminotransferase <2.5 times the upper limit of normal. Patients with other active malignancies or uncontrolled concomitant diseases were excluded. Written informed consent was obtained from all participants after they had received a full explanation of the nature of the study. The study was approved by the institutional review board of Nagoya University Hospital and all other hospitals belonging to the Chubu Clinical Oncology Group that participated in this multicenter trial.

Pretreatment evaluation, treatment plan, and dose attenuation

At baseline, a complete medical history was taken, and a physical examination was performed. Laboratory assessment at baseline included blood cell counts, serum chemistry profiles, serum tumor markers (carcinoembryonic antigen, CA19-9), and urinalysis. Patients also underwent a baseline electrocardiographic examination and computed tomography (CT) scans of the chest, abdomen and pelvis.

Patients received S-1 at an oral dose of 40 mg per square meter of body-surface area twice daily for 4 weeks, followed by 2 weeks without chemotherapy. Patients with a body-surface area of less than 1.25 m^2 received 80 mg daily; those with a body-surface area of 1.25 m^2 to less than 1.5 m^2 received 100 mg daily; and those with a body surface area of 1.5 m^2 or greater received 120 mg daily. This 6-week cycle was repeated in an outpatient setting under medical supervision until disease progression, unacceptable adverse events, or the patient's withdrawal of consent. If the patients had either ≥grade 3 hematologic toxicity or ≥grade 2 non-hematologic toxicity, the daily dose of S-1 was decreased from 120 mg to 100 mg, from 100 mg to 80 mg, or from 80 mg to 50 mg. If adverse events tended to occur during the third or fourth week of S-1 treatment, the schedule could be modified to a 3-week cycle, in which patients were given S-1 for 2 weeks followed by 1 week of rest.

Disease status was assessed once every 3 months on the basis of serum tumor markers and at least once every 6 months by CT scanning. Adverse events were monitored by interviews, blood chemical profiles, and blood cell counts once every 2 weeks. All toxic effects were graded according to National Cancer Institute Common Toxicity Criteria (NCI-CTC; version 2.0).

Biostatistics

Data on 30 consecutive patients with gastric cancer who underwent surgery from 1995 to 1999 and had positive cytologic results of peritoneal washings (CY1) as the sole cause of noncurative resection were retrospectively retrieved from the database of Aichi Cancer Center Hospital, a high-volume center in the Aichi district of Japan. Survival data were analyzed for these patients to provide a historical control. The 2-year survival rate of this cohort was 13.3% (90% confidence interval, 3.1–23.5%). The 2-year survival rate of patients with advanced/metastatic gastric cancer who were given single-agent S-1 at National Cancer Center East (a high-volume center that participated in late phase II trials of S-1 before the drug became available to community hospitals) was 36%. On the basis of these data, we assumed that the 2-year survival rate of our series would be 36% and expected that the lower limit of the 90% confidence interval would exceed 23.5% (i.e., the upper limit of the 90% confidence interval for the historical control) to calculate the required number of patients. We estimated that 50 patients would have to be enrolled to achieve a 2-year survival rate of 36% (18/50) with a 90% confidence interval of 24.8–47.3% and designated the 2-year overall survival rate as the primary endpoint of this study. The secondary endpoints were safety and the time to treatment failure. Survival analyses were carried out with the Kaplan–Meier method.

Results

Patient population

Forty-eight patients were enrolled between February 2002 and July 2006. The demographic and clinicopathologic characteristics of the patients are shown in Table 1. One of the patients was mistakenly enrolled despite having no cytologic evidence of cancer cells in peritoneal washings (CY0). This patient was ineligible and excluded from further analysis. Resections were classified as palliative (R1) according to the results of cytologic examination of peritoneal washings in all but one patient who had a positive resection margin on microscopic examination of the resected specimen in addition to the CY1 status. This patient was included in the survival analysis; it was assumed at the time that CY1 would be a stronger prognostic determinant than a positive resection margin. The patient died 561 days after surgery. Another patient who died of myocardial infarction 5 days after starting treatment with S-1 was included in the analysis of survival but not of adverse events; this death was considered unlikely to have been treatment-related.

Of the 47 eligible patients, 7 patients had peritoneal deposits, which were co-resected at surgery (Table 1). Seven patients were intraoperatively confirmed to have invasion to adjacent organs (T4), and 38 others had serosal invasion.

Table 1
Patient demographics ($n = 47$).

	No.	%
Age, years		
Mean (range)	63 (39–79)	
Gender		
Female	15	32
Male	32	68
ECOG Performance Status		
0	35	74
1	12	26
2	0	0
pT categories		
1	2	4
2	2	4
3	37	79
4	6	13
pN categories		
0	5	11
1	11	23
2	25	53
3	6	13
Peritoneal deposits		
No	40	85
Yes	7	15
Histological type		
Undifferentiated	25	53
Differentiated	18	38
Mucinous	4	9
Surgery		
Total gastrectomy	19	41
Distal gastrectomy	27	57
Pancreaticoduodenectomy	1	2
Nodal dissection		
D0	1	2
D1	13	28
D2	31	66
D3	2	4

All but five patients were confirmed to have nodal involvement on pathological examination; six patients had metastasis to the paraaortic lymph nodes.

Responses and survival

Owing to the unique eligibility criteria, objective response was not assessable in any patient. Overall survival and progression-free survival are shown in Fig. 1. Median overall survival time was 705 days, and progression-free survival time was 376 days. The 2-year survival rate was 47% (90% confidence interval, 34.8–58.8%). The lower limit of the 90% confidence interval exceeded the upper limit of the confidence interval for the historical control (23.5%). The most frequent pattern of disease recurrence was peritoneal carcinomatosis, occurring in 26 patients. Other patterns of recurrence were hepatic in 4 patients, lymphatic in 4, locoregional in 2, pulmonary in 1, and osseous in 1. Median survival after confirmation of recurrence was 183 days. Median time to treatment failure was 288 days (Fig. 2). There was no difference in survival between the 7 patients with visible peritoneal

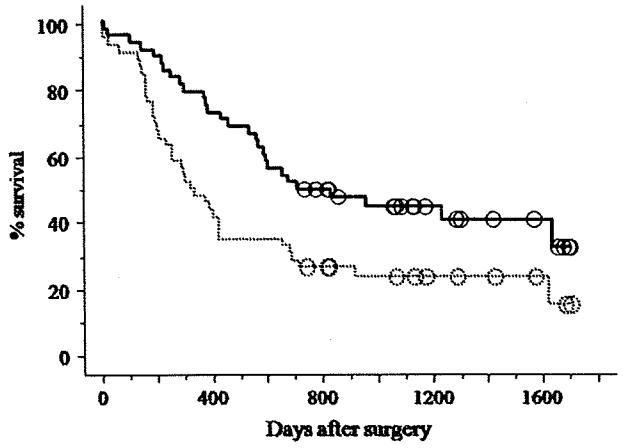

Figure 1. Overall survival (solid line) and progression-free survival (dotted line) of patients with gastric cancer who had free cancer cells in the peritoneal cavity and underwent surgery followed by S-1 monotherapy. Median survival was 705 days with a 2-year survival rate of 47%. Progression-free survival was 376 days.

deposits in addition to positive cytologic results and the other 40 patients with only positive cytologic results.

Compliance, dose intensity, and toxicity

Two patients did not start chemotherapy within 6 weeks after surgery because of surgical complications; however, treatment was eventually started in all enrolled patients. S-1 monotherapy was terminated within 1 year because of toxicity in seven patients. In four of these patients, S-1 was withdrawn within the first 6-week cycle. The dose of S-1 had to be reduced by one level in 7 of the 40 patients who tolerated treatment. The treatment schedule was switched to a 3-week cycle in two of the seven patients who underwent dose reduction and in one other patient. Treatment was generally well tolerated. The toxicity profile is shown in Table 2. Grade IV toxicity occurred in only one patient, who was among the four patients who discontinued therapy during the first cycle. Neutropenia was the most common grade III toxicity, and anorexia and nausea were the commonest reasons for drug withdrawal.

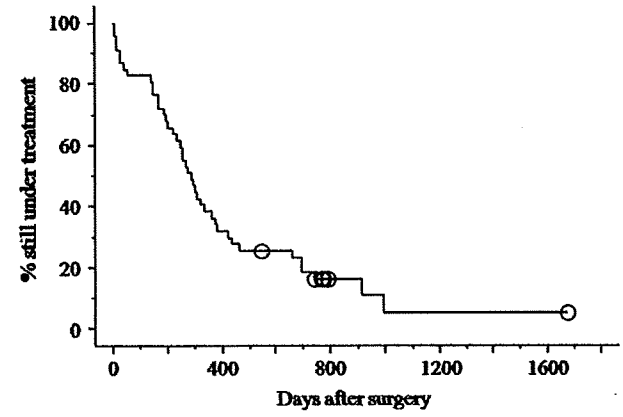

Figure 2. Time to treatment failure in patients with gastric cancer who had free cancer cells in the peritoneal cavity and underwent surgery followed by S-1 monotherapy. Median time to treatment failure was 288 days.

Table 2
Adverse events in postoperative S-1 monotherapy ($n = 46$).

	No. of patients			% ≥Grade 3
	Grade 2	Grade 3	Grade 4	
Leukocytopenia	15	1	0	2
Neutropenia	12	6	0	13
Anemia	20	3	0	7
Thrombocytopenia	1	0	0	0
	No. of patients			% ≥Grade 2
	Grade 2	Grade 3	Grade 4	
Anorexia	7	3	1	24
Nausea	4	4	0	17
Vomiting	2	0	0	4
Stomatitis	6	0	0	13
Diarrhea	8	0	0	17
AST/APT	2	2	0	9
Bilirubin	3	6	0	20
Creatinine	1	0	0	2
Pigmentation	9	0	0	20
Eruption	5	1	0	13
General malaises	1	3	0	9

Discussion

S-1 as a logical candidate for treatment of CY-1 stage gastric cancer

CY1-stage disease has not been studied extensively in clinical trials, despite the clear prognostic value of cytologic examination.[7] The main reason for the paucity of studies has been the lack of measurable lesions and consequent difficulty in evaluating treatment response. The optimal treatment strategy for patients who have gastric cancer with CY1 status thus remains to be defined. S-1 is an oral fluoropyrimidine that has had very high response rates when given as a single agent in the Far East.[12,13] The efficacy and safety profile of S-1 after gastrectomy have been evaluated in a pivotal phase III trial in Japan.[15] In that trial, postoperative adjuvant chemotherapy with S-1 was also suggested to reduce the incidence of peritoneal recurrence.[15] We have previously studied the activity of S-1 in an *in vivo* model of peritoneal metastasis and reported that S-1 given early after the dissemination of gastric cancer cells may be effective.[16] S-1 monotherapy may therefore be a useful treatment option for patients with CY1 status in community hospitals. Clinical data supporting its efficacy in this subgroup of patients had been lacking, however, and a prospective study was awaited.

Difficulties in designing a clinical trial for CY1 stage cancer

Since patients with CY1 status have no measurable lesions, the endpoint of a clinical trial had to be survival time. Ideally, a randomized controlled study comparing S-1

with another treatment should have been performed to objectively evaluate outcomes. However, the current edition of the Japanese Classification of Gastric Carcinoma clearly defines surgery in patients with CY1 status as noncurative resection,[8] and it was considered unethical to treat a control group by surgery alone. Since there was no established therapy when this study was designed, we decided to perform a one-arm trial of S-1 to search for an effective control treatment. Subsequently, new regimens that appear to be effective against advanced/metastatic disease could then be compared with S-1 monotherapy in randomized trials to decide which is best suited for standard treatment. In this initial step in the search for a standard regimen for gastric cancer with CY1 status, we thus had to compare S-1 with a historical control. This is of course an important limitation of our study, but was considered unavoidable in view of ethical and clinical issues.

Comparison of S-1 monotherapy with a historical control

The historical data were obtained from a local, high-volume cancer center, which was a member of the study group and maintains a reliable prospective database. During the era of the previous edition of the Japanese Classification of Gastric Carcinoma, cytologic examination was considered an investigational procedure and was not incorporated in the staging scheme. The standard surgical procedure for patients with CY1 status at that time was D2 surgery, similar to that recommended in the protocol of the present study. S-1 was not available, and patients postoperatively received older drugs such as mitomycin and/or 5-fluorouracil[17] or were observed with no further treatment until disease progression. The 2-year survival rate of patients with CY1 status was only 13.3%. At present, not only S-1, but also taxanes and irinotecan can be used for second-line chemotherapy.[18] These new, improved treatments and progress in medicine in general are two reasons why many would argue against the use of a historical control. However, it is difficult to deny that S-1 had a positive effect on outcomes, given that the 2-year rate of progression-free survival, not overall survival, was well over 20%. Several patients remain disease-free more than 2 years after surgery, and there is hope that some of these patients eventually might be cured. Since peritoneal carcinomatosis is not easy to detect, however, longer follow-up is needed for confirmation. The protocol did not specify conditions for stopping treatment, other than the disease recurrence, unacceptable adverse events, or the patient's refusal. Several of the long-term survivors are still receiving S-1. The outcomes of these patients after the withdrawal of S-1 are another important issue.

Applicability of our data to countries outside of the Far East

S-1 is a potentially toxic drug among whites because of polymorphic differences in the CYP2A6 gene.[19] Potential survival benefits of S-1 over 5-fluorouracil in Western patients are now being evaluated in a global phase III trial comparing S-1 plus cisplatin with a conventional combination of 5FU and cisplatin in patients with advanced/metastatic gastric cancer. In the meantime, the favorable results of the present trial may apply only to Japanese or other Asian patients residing in the Far East.

The protocol for this trial did not require that the results of cytologic examination were obtained during surgery. We presume that this information was not available for the two patients who underwent D3 dissection, but was available for the one patient who underwent D0 dissection. With the exception of these three patients, the recommendations in the protocol for the extent of lymphadenectomy were closely followed. Owing to the recent Western success with the "modified" D2 surgery,[20] splenectomy was not required in our trial. Spleen-preserving surgery for cancer arising in the upper third of the stomach is formally classified as D1 dissection according to the Japanese Classification, and this is the primary reason why D1 dissection was performed in a high proportion of patients (13/47, 28%). If we include the 31 patients who underwent D2 dissection, 94% (44/47) of our subjects underwent either modified or stringent D2 dissection, indicating good compliance with the study protocol as compared with the INT0116 study in the United States.[6] D2 dissection has been shown to result in good local control,[21] but is not routinely performed outside of the Far East. This is another reason that the results of the present trial may not be universally applicable.

Memorial Sloan Kettering Cancer Center is one hospital in the United States where D2 dissection is often performed. Interestingly, this Center retrospectively identified 24 patients with CY1 status among those who received radical surgery between 1993 and 2002. The median survival time of these patients was 14.8 months, with a 2-year survival rate of 30%.[10] Although inferior to the lower limit of the 90% confidence interval in our study, their survival rate was superior to the upper limit of the 90% confidence interval of the historical control. This finding suggests that outcomes similar to those in our study can be expected in the West when optimal surgery is combined with state-of-the-art perioperative treatment.

Clinical characteristics of patients with CY1-stage gastric cancer

To our knowledge, this is the first prospective clinical trial of patients with CY1 status to be reported. It has provided an opportunity to examine the clinical characteristics of this subgroup. Most patients with CY1 status had locally advanced disease: 91% had $\geq$T3-stage disease, and 89% had lymph node metastasis. As expected, peritoneal carcinomatosis was the commonest pattern of treatment failure. In our trial, patients with a small number of peritoneal deposits were eligible, provided that these deposits had been resected to avoid R2 resection. Patients who underwent

extensive cytoreductive surgery by total peritonectomy[22] were not included; our subjects had not participated in clinical trials of such procedures. Survival of the seven patients in our study who had peritoneal deposits at surgery was, as expected, similar to that of the other patients, who had no visible peritoneal metastases. Thus, the decision to include patients with peritoneal deposits as subjects seems justified.

Concluding remarks

In our study, the outcomes of patients who had gastric cancer with CY1 status were better than initially expected, but remained poor. Future treatments are now being developed, including locoregional therapy through indwelling catheters.[23,24] Since patients with CY1 status have locally advanced disease with potential for other patterns of treatment failure, however, more intensive combination chemotherapy may be necessary. A randomized phase III trial has recently shown that a combination of S-1 and cisplatin is superior to S-1 monotherapy in patients with advanced/metastatic gastric cancer.[25] We are currently studying the feasibility of postoperative treatment with S-1 and cisplatin. However, this combination may be too toxic to start shortly after radical gastrectomy. Some have proposed that diagnosis with staging laparoscopy followed by preoperative chemotherapy[26] may prove to be the best option. Various clinical trials are now being planned to assess the best ways to manage advanced gastric cancer with CY1 status. Monotherapy with S-1 can now be considered a promising active control for such trials conducted in the Far East.

Conflict of interest

The authors state that they have no conflict of interest.

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別刷

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進行胃癌術後補助化学療法としてS-1の投与方法についての検討

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●原 著●

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Examination of S-1 Therapy for Adjuvant Chemotherapy in Patients with Advanced Gastric Cancer: Koshi Matsui, Atsushi Nashimoto, Hiroshi Yabusaki, Satoru Nakagawa, Tatsuya Nomura, Yasumasa Takii, Yoshiaki Tsuchiya and Otsuo Tanaka (*Dept. of Surgery, Niigata Cancer Center Hospital*)

Summary

Purpose: In our department, S-1 has been administered for 1 year as postoperative adjuvant chemotherapy for advanced gastric cancer since 2000. It was started by a standard dosage of 4-week administration with 2 weeks rest since 2000 (A group). However, since 2002, it was changed with the expectation of the reduction of side effects by 2-week administration with a one-week rest (B group). Treatment continuity, adverse events and efficacy in both A and B groups were examined. Subjects: The subjects were 96 patients with fStage Ⅱ, ⅢA and ⅢB who were treated with S-1 after curative operation between 2000 and 2006. Results: The percentage of patients who complied with the dosing instructions completely during a 1-year period was 70.2% in the A group and 77.6% in the B group. The incidence of Grade 3 and 4 toxicity was 1 nausea, 2 appetite loss, 1 neutropenia, 1 liver dysfunction in the A group and 1 nausea, 3 neutropenia in the B group, against, 76.6% in the A group and 44.9% in the B group, respectively, in the case of discontinuation, Thus, the trend in significantly high incidence in the A group was recognized. The 3-year survival rates in cases with a case of over 3 years were 88.5% in the A group and 87.5% in the B group, i. e., no difference. Conclusion: Though the difference was not recognized in continuation rate, efficacy and adverse events in both A and B groups, there were significantly few withdrawal cases in the B group, and it seemed to be an effective medication method. Key words: Gastric cancer, Adjuvant chemotherapy, S-1 (*Received Jul. 28, 2008/Accepted Nov. 27, 2008*)

要旨 目的: 当科では進行胃癌に対する術後補助化学療法として2000年よりS-1単剤を1年間投与している。当初，4週投与2週休薬（A群）の標準投与法で開始したが，2002年からは副作用の軽減を期待して2週投与1週休薬（B群）に変更した。今回A，B両群における治療継続性，有害事象および有効性について比較検討した。対象: 2000～2006年までに根治手術が行われたfStage Ⅱ，ⅢA，ⅢBに対して術後S-1を投与した96例（A群47例，B群49例）である。結果: 1年間の内服継続率はA群70.2%，B群77.6%とB群が高率であったが有意差はみられなかった（p=0.56）。grade 3以上の有害事象はA群で悪心1例，食欲不振2例，好中球減少1例，肝機能障害1例，B群では悪心1例，好中球減少3例であり，ほとんど差は認められなかった。しかし，休薬した症例はそれぞれ76.6%と44.9%で，A群で有意に多い傾向を認めた（p=0.03）。3年以上経過した症例（A群44例，B群16例）での3年生存率はA群88.5%，B群87.5%で差はなかった。結論: S-1の2週投与1週休薬法は4週投与2週休薬法と比較して継続率，有効性および有害事象に差は認めなかったが，休薬症例が有意に少なく，有効な投与方法であると考えられた。

はじめに

進行胃癌術後の補助化学療法は，ACTS-GCの中間報告よりS-1の有用性が報告された[1]。当科でも2000年から術後補助化学療法としてS-1の投与を積極的に行ってきた。当初，標準投与法である4週間投与2週間休薬にて行っていたが，内服してから2週間後より副作用の発現にてコンプライアンスが低下する傾向があった。そのため，副作用の発現しやすい2～3週目に休薬することにより副作用が軽減され，コンプライアンスが

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表1 背景因子

		A群（n=47）	B群（n=49）
性別（男性：女性）		31：16	34：15
年齢		64（38～76）	60（33～78）
切除法	全摘	14（29.8%）	17（34.7%）
	幽門側	33（70.2%）	32（65.3%）
深達度	T1	2（4.3%）	1（2.0%）
	T2	22（46.8%）	26（53.1%）
	T3	23（48.9%）	22（44.9%）
リンパ節転移	N0	3（6.4%）	3（6.1%）
	N1	30（63.8%）	30（61.2%）
	N2	14（29.8%）	16（32.7%）
fStage（胃癌取扱い規約）	Ⅱ	22（46.8%）	21（42.9%）
	ⅢA	18（38.3%）	22（44.9%）
	ⅢB	7（14.9%）	6（12.2%）

表2 治療継続率

期間	A群（n=47）			B群（n=49）			ACTS-GC（n=517）
	継続率	中止理由		継続率	中止理由		継続率
		有害事象	再発		有害事象	再発	
3か月	78.70%	10	0	89.80%	5	0	87.40%
6か月	76.60%	0	1	83.70%	1	1	77.90%
9か月	70.20%	2	1	77.60%	0	4	70.80%
12か月	70.20%	0	0	77.60%	0	0	65.80%

上昇することを予測し，2002年より2週間投与1週間休薬という投与方法に変更した。

今回われわれは，補助化学療法としてS-1の2週投与1週休薬投与方法の有用性を4週投与2週休薬投与方法と比較検討したので報告する。

Ⅰ．対象・方法

2000～2006年までの胃癌手術症例で，①総合的根治度AまたはB，②総合所見でStageⅡ，Ⅲ，③手術以外の前治療が実施されていない，④年齢80歳以下を対象とした96例。

S-1投与方法：手術後S-1（80 mg/m^2）をA群：4週間連日投与2週間休薬，B群：2週間連日投与1週間休薬で1年間投与する。

有害事象：NCI-CTC ver.3に準じて評価する。評価項目は血液毒性として白血球数，血色素量，好中球数，血小板数，AST，ALT，血清総ビリルビン，血清クレアチニン。非血液毒性として悪心，嘔吐，食欲不振，下痢，口内炎，皮疹，倦怠感とした。

中止基準：転移・再発が確認された場合，あるいは有害事象により医師がS-1投与の継続を困難と判断した場合。

休薬基準：grade 2以上の白血球数および血小板数の減少。その他の血液毒性がgrade 3以上の場合。grade 2以上の消化器症状。患者からの服薬休薬の申し出があった場合。休薬後は有害事象が改善した時点で再開し，場合によっては投与量の減量を考慮する。減量基準は120→100，100→80，80→50 mg/body/dayとしており，ACTS-GCと同様としている。

生存率の算出はKaplan-Meier法，2群間の検定はχ^2検定にて行った。

Ⅱ．結　果

4週投与2週休薬（A群）47例。2週投与1週休薬（B群）49例。

背景因子（表1）。A群，B群それぞれ男女比31：16，34：15，年齢（中央値）64，60歳であり，切除法，深達度，リンパ節転移，Stage（胃癌取扱い規約）について両群間に有意差は認めなかった。

1．継続率

術後1年間のS-1内服継続率はA群で70.2%，B群で77.6%であり，有意差はないもののB群が高い傾向を示した（表2）。休薬率はA群76.6%，B群44.9%と有意差をもってA群で高かった（p=0.03）。休薬理由はgrade 2以上の骨髄抑制によるものがA群で11例（23.4%），B群で11例（22.4%）と差がなかった（表

表3　休薬，減量

		A群（n=47）	B群（n=49）	p値
休薬率		76.60%	44.90%	0.03
休薬理由	grade 2以上の骨髄抑制	11（23.4%）	11（22.4%）	1
	grade 2以上の消化器症状	13（27.7%）	4（8.2%）	0.025
	本人の希望（倦怠感など）	6（12.8%）	6（12.2%）	1
	その他の副作用	9（19.1%）	3（6.1%）	0.105
減量		2（0.04%）	2（0.04%）	1

表4　有害事象

	A群（n=47）				B群（n=49）			
	grade				grade			
	1	2	3	4	1	2	3	4
白血球減少	11（23.4）	6（12.8）	0（0）	0	7（14.3）	12（24.5）	0（0）	0
血色素減少	33（70.2）	5（10.6）	0（0）	0	37（75.5）	7（14.3）	0（0）	0
好中球減少	6（12.8）	9（19.1）	1（2.1）	0	5（10.2）	7（14.3）	3（6.1）	0
血小板減少	13（27.7）	1（2.1）	0（0）	0	17（34.7）	1（2.0）	0（0）	0
AST上昇	17（36.1）	0（0）	1（2.1）	0	19（38.8）	0（0）	0（0）	0
ALT上昇	15（31.9）	1（2.1）	1（2.1）	0	14（28.6）	2（4.1）	0（0）	0
T-Bil上昇	8（17.0）	3（6.4）	0（0）	0	5（10.2）	8（16.3）	0（0）	0
血清Cre上昇	2（4.3）	0（0）	0（0）	0	3（6.1）	0（0）	0（0）	0
悪心	16（34.0）	1（2.1）	1（2.1）	0	17（34.7）	1（2.0）	1（2.0）	0
嘔吐	5（10.6）	1（2.1）	0（0）	0	7（14.3）	1（2.0）	0（0）	0
食欲不振	18（38.3）	9（19.1）	2（4.3）	0	24（49.0）	3（6.1）	1（2.0）	0
下痢	22（46.8）	6（12.8）	0（0）	0	25（51.0）	2（4.1）	0（0）	0
口内炎	19（40.4）	2（4.3）	0（0）	0	12（24:5）	1（2.0）	0（0）	0
皮疹	25（53.2）	0（0）	0（0）	0	20（40.8）	4（8.2）	0（0）	0
倦怠感	16（34.0）	1（2.1）	0（0）	0	28（57.1）	2（4.1）	0（0）	0

3)。しかし，grade 2以上の消化器症状による休薬がA群で13例（27.7%），B群で4例（8.2%）と有意にA群で多かった。内容は食欲不振，下痢によるものが最も多かった。減量はそれぞれ2例ずつで行われており，全例完遂することが可能であった。中止理由としては有害事象による患者希望が最も多く，A群で9例（19.1%），B群で4例（8.2%）であった。医師の判断で中止したのがA群3例（6.4%），B群2例（4.1%）であった。転移・再発による中止例はA群2例（4.3%），B群5例（10.2%）とB群に多かった。転移・再発部位は肝臓が3例，リンパ節が3例，腹膜播種が1例であった。

2．有害事象

両群での有害事象を検討した（表4）。

1）血液毒性

grade 3の好中球減少をA群で1例（2.1%），B群で3例（6.1%）認めた。発熱を伴う好中球減少はなく，G-CSF製剤を用いた症例は認めなかった。一方，貧血や血小板減少は大部分がgrade 2以下で輸血などの治療を要するものはなく，休薬のみで改善し，中止に至った症例は認めなかった。また，A群にてgrade 3の肝障害を認め，中止に至った症例を1例認めた。

2）非血液毒性

休薬の目安となるgrade 2以上の食欲不振をA群で11例（23.4%），B群で4例（8.2%）認め，有意差までには至らなかったがA群で高頻度に認めた（p=0.07）。grade 2以上の下痢に関してもA群で6例（12.8%），B群で2例（4.1%）とA群で高頻度（p=0.24）であり，A群において消化器症状が多い傾向があった。逆に皮疹はB群4例（8.2%）のみで認めた（p=0.13）。grade 3以上の悪心を両群それぞれ1例ずつ認めた。

有害事象の発生率はこれまでの報告とほぼ同様で忍容性も良好であった。

3．生存率，無再発生存率

術後3年以上経過している症例のみを検討の対象としたところ，A群44例，B群16例であった。生存率に関して両群間に有意な差は認められず（p=0.99），3年生存率はA群88.5%，B群87.5%であった（図1）。無再発生存率にも同様に有意な差はなく（p=0.82），A群72.2%，B群81.3%であった。

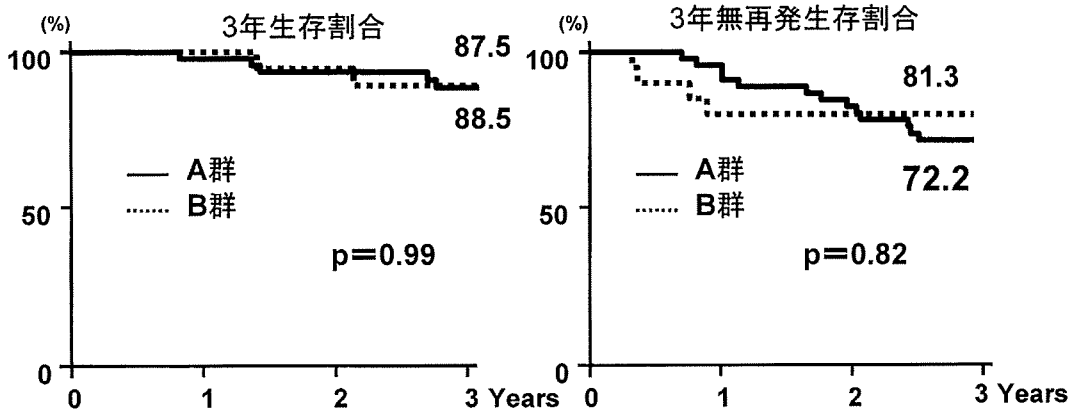

図 1 追跡期間中央値
A 群:1,360 日（290～2,711）n=47，B 群:1,172 日（500～1,691）n=16

Ⅲ. 考 察

胃癌の術後化学療法の有用性に関しては賛否両論があった。しかしながら，ACTS-GC の中間報告の結果を受け，S-1 による術後補助化学療法が標準治療として受け入れられるようになりつつある。実際，胃癌治療ガイドラインにおいても標準治療としての位置付けが行われようとしている。そこで，術後補助化学療法を行うに当たり，薬剤の忍容性と有害事象の発現および程度が問題となってくる。

木村らは進行再発胃癌に対して S-1 の投与方法について検討しており，S-1 の 2 週投与 1 週休薬法は 4 週投与 2 週休薬法に比べ副作用の発現頻度が低く，6 か月間での服薬完遂率が高いと報告している[2]。また，ACTS-GC においても副作用に対して減量だけでなく，コース投与期間短縮の基準として 2 週投与 1 週休薬を推奨している。そこで当科では S-1 の標準投与法である 4 週投与 2 週休薬という投与方法に対して，コンプライアンスと QOL の上昇を期待して，2 週投与 1 週休薬という投与方法に変更した。その投与方法の変更により，実際に効果の減弱がなく副作用が軽減されたかどうか比較検討した。

自験例の継続率の結果を ACTS-GC と比較検討した。継続率では A 群，B 群および ACTS-GC の治療中止例の割合は 70.2，77.6，65.8%と B 群で最も継続率が良好であった。背景因子に差はなく，休薬や中止の基準もほぼ同様であることから，2 週投与 1 週休薬の投与方法が 4 週投与 2 週休薬よりコンプライアンスの良好な方法と思われる。

S-1 の主な有害事象は白血球減少，好中球減少，血色素減少，血小板減少などの骨髄抑制や，食欲不振，悪心，嘔吐，下痢などの消化器症状の他に皮膚症状，全身倦怠感がある。後期臨床第Ⅱ相試験での二つのグループの副作用発現率はそれぞれ 78.4，72.0%であり，grade 3 以上の発現率は 19.6，10.0%と報告している[3,4]。今回の検討では grade 2 以上の骨髄抑制が A 群にて 14 例（29.8%），B 群にて 18 例（36.7%）でみられたが，骨髄抑制が理由で継続中止とした症例は認めなかった。中止あるいは休薬の理由としては消化器症状が多く，grade 2 以上の悪心，嘔吐，食欲不振，下痢などがみられたのは A 群で 15 例（31.9%），B 群にて 7 例（14.3%）と A 群において高率であり（p=0.07），A 群のコンプライアンスの低下につながっていた。特に食欲不振においてその傾向は強かった。ただし，消化器症状の訴えがまったくなかった割合は A 群で 14.9%，B 群で 14.3%とほとんど差がなかった。これは，消化器症状が一度出現すると，4 週投与 2 週休薬ではその症状が増悪しやすい傾向があることを示している。つまり，副作用が出現しやすい 2，3 週目に休薬となる 2 週投与 1 週休薬による投与方法がコンプライアンスの上昇の理由となっている。

木村らは進行再発胃癌に対し，S-1 を 4 週投与 2 週休薬法と 2 週投与 1 週休薬法での有効性を比較検討しているが，奏効率に有意差はなかったと報告している[2]。原らは胃切除範囲および郭清度の違いで有害事象の発現率に差があり，手術侵襲と有害事象の発現との関係を示唆しているが[5]，今回の検討ではそのような傾向は認められず，手術侵襲が大きい症例においても grade 3 以上の有害事象は低率であり，コンプライアンスも良好であった。

S-1 の 2 週投与 1 週休薬法は副作用が軽減され，高い継続率が得られることにより QOL が高く維持される方法である。今回の検討においても，S-1 の投与回数の中央値は A 群で 202 回，B 群で 230 回であった。高い継続率と低い休薬率により標準投与方法と同等の有効性が得られる有効な投与方法であると考えられた。

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● 特 集 ● がんの適切なフォローアップ計画

胃癌の適切なフォローアップ計画

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Proper Follow-up Schedule after Curative Gastric Surgery: Atsushi Nashimoto, Hiroshi Yabusaki and Satoru Nakagawa (*Division of Gastric Surgery, Niigata Cancer Center Hospital*)

Summary

Although the prognosis of gastric cancer after R0 resection is considered to be comparatively satisfactory, some patients experience cancer recurrence according to their stage. Recurrence patterns after curative gastrectomy and follow-up surveillance were studied. An analysis was done in about 307 (8.0%) patients with recurrences of 3,861 primary gastric cancers who underwent R0 resection with sufficient lymph node dissection from 1990 to 2006.

Results: The median age was 64 years old, and there were 211 men and 96 women. The recurrence rates were hematological 41%, peritoneal 33%, and remote lymph nodal 24%, though peritoneal recurrence was most frequent in references. There were many peritoneal and remote lymph nodal recurrences in undifferentiated adenocarcinomas, and hematological recurrences in differentiated adenocarcinomas. In pT1, hematological recurrences were 83% and lymph nodal recurrences were 17%, even after 5 years. In more than half, remnant stomach cancers were found, and these cases underwent surgery again 5 years after primary surgery. The frequency of peritoneal recurrence was increased remarkably in pT3 and pT4. The proportion of recurrence was 77% within 2 years and 91% within 3 years, respectively. There was no difference between lymph nodal, hematological and peritoneal recurrence in survival time after primary surgery and even after recurrence. Referring to these results, follow-up surveillance plans for early and advanced gastric cancers were made. Surveillance was to be continued for 10 years after surgery in the early cancers and 5 years after surgery in the advanced cancers. Moreover, a mass survey or complete medical checkup was recommended at 5 years after surgery. A standard follow-up plan will be made soon for early and advanced gastric cancer patients, respectively, though it is not necessarily the same in several institutes. There is no consensus yet regarding the intensive follow-up plan after R0 resection, because the evidence of efficacy is not yet confirmed. In conclusion, an intensive scientific investigation of the follow-up plan is required to determine wether or not there are survival benefits.

Key words: Gastric cancer, Curative gastric surgery, Follow-up schedule, Critical path, Recurrence pattern, Surveillance, Corresponding author: Atsushi Nashimoto, Division of Gastric Surgery, Niigata Cancer Center Hospital, 2-15-3 Kawagishi-cho, Chuo-ku, Niigata 951-8566, Japan

要旨 治癒切除胃癌術後の再発形式，再発時期および定期的なフォローアップ計画につき文献的な考察を加え検討した。対象は初発単発治癒切除胃癌3,861例中，術後再発が認められた307例（8.0%）である。再発形式は血行性再発が最も多く，腹膜再発，リンパ節再発，局所再発の順であった。低分化型腺癌は腹膜再発が多く，分化型腺癌では血行性再発が3/4を占めた。pT1では90%が血行性再発，10%がリンパ節再発であった。腹膜再発はpT3から急に増加した。1年以内では血行性再発と腹膜再発がほぼ同数であった。早期胃癌では2年以内に50.0%が再発し，3年以内に88.9%が再発していた。一方，進行胃癌では2年以内に79.2%が再発し，3年以内に90.7%が再発していた。術後の50%生存期間は，リンパ節再発，血行性再発，腹膜再発に差はなく，再発後の生存期間にも差はみられなかった。この結果を踏まえて，また今後地域連携パスが普及することを考慮して，Stage Ⅰ胃癌およびStage Ⅱ～ⅢB胃癌に対する術後フォローアップ計画を作成した。進行胃癌は術後5年まで，早期胃癌は術後10年まで続けるが，5年以降は毎年基本検診，職場検診や人間ドックを積極的に受けるよう指導することとした。定期的な術後フォローアップによる胃癌再発例の延命効果についてはいまだcontroversialである。今後，術後フォローアップが延命に寄与しているか否かについては科学的に検証していく必要がある。

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はじめに

胃癌の治療成績は向上しているが，依然として進行胃癌は高率に再発している[1-3]。注意深い術後フォローアップにより，できるだけ早期に再発を発見することで残胃の局所再発，一部の肝・肺転移および腹部大動脈周囲リンパ節再発巣を外科的に切除できる場合もある[4]。しかし，腹膜播種や複合再発のように手術が不可能なことが圧倒的に多く，主に抗癌剤による多剤併用療法や集学的治療が行われている。しかし，再発症例を治癒させることは困難であるのが現状である。当科でも時代的な変遷はあるが，厳重に術後の定期的なフォローアップを続けてきた[5,6]。その目的は胃切除後障害に対する生活指導と治療，再発していないことの確認および再発しても早期発見，早期治療することにより治癒をめざすことである。さらに残胃の癌を治療することや異時性他臓器重複癌の発見なども考慮した。

今回，胃癌治癒切除後の再発の実態と遠隔成績を検討するとともに，定期的なフォローアップ計画の意義について検討した。

Ⅰ．対象と方法

当院で1990～2006年までに経験した初発単発治癒切除胃癌（同時性多発胃癌，術中腹腔内細胞診陽性（CY1）例および残胃の癌を除く）3,861例中，手術後再発を認めた307例（8.0%）を対象に術後の初発再発形式，再発時期と遠隔成績につき検討を加えた。なお，再発形式は初発部位とし，他部位同時性再発例は主たる再発部位を初発再発形式とした。

Ⅱ．結　果

1．再発例の初回手術時臨床病理学的因子

男性211例，女性96例で年齢の中央値は64（19～95）歳であった（表1）。肉眼型は3型，4型で57%を占め，組織型は分化型121例，未分化型186例であった。深達度はpT1 18例，pT2 94例，pT3，pT4 195例（64%）であり，fStage Ⅰ 32例（10%），fStage Ⅱ 50例（16%），fStage Ⅲ 118例（38%）fStage Ⅳ 107例（35%）とfStage Ⅲ/Ⅳが73%を占めていた。

2．早期胃癌の再発

再発率は0.8%（18/2,354）であり，分化型，未分化型ともに0.8%（血行性80%，リンパ行性20%）であった。再発率は初回手術時にリンパ節転移陰性例0.4%，陽性例5.1%であり，リンパ節転移陰性例ではほとんど再発しない（図1）。80%が血行性再発，20%がリンパ節再発であり，腹膜再発は1例もなかった。再発時期は術後2年以内に50%，術後3年以内に88.9%が再発していたが，術後5年経過後の再発も5%に認められた（図2）。術後1年以内の再発はすべて血行性再発であった。

3．進行胃癌の再発

1）再発形式

進行胃癌の再発率は19.2%で，pT2 11.3%，pT3，pT4 28.3%であった（図3）。血行性再発（肝，骨，肺，皮膚，その他）が最も多く，以下腹膜再発，リンパ節再発，局所再発の順であった。組織型別では分化型腺癌では再発率15.5%（108/697）で，血行性再発（肝転移が最も多い）が6割を占め，以下腹膜再発，リンパ節再発の順であった。一方，低分化型腺癌では再発率22.5%

表1 背景因子

性別	男性/女性	211/96
年齢	中央値（範囲）	64（19～95）
肉眼型	0/1/2/3/4	34/12/87/116/58
組織型	分化型/未分化型	121/186
術式	幽切/全摘/他	149/150/8
深達度	pT1（SM）/2/3/4	18/94/158/37
リンパ節転移	pN0/pN1/pN2/pN3	42/98/91/76
fStage	Ⅰ/Ⅱ/Ⅲ/Ⅳ	32/50/118/107

（n=307）

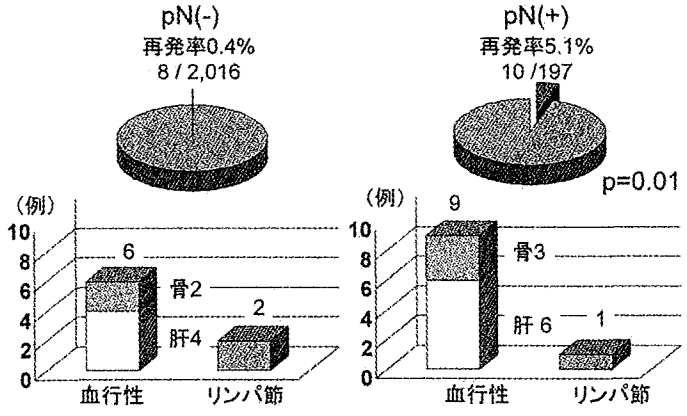

図1 早期癌の再発状況

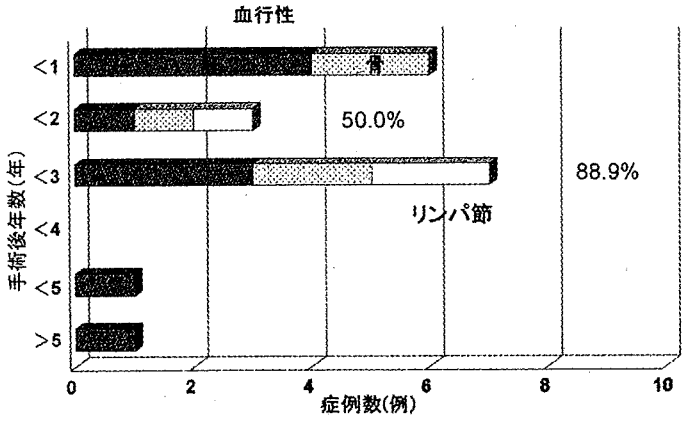

図 2 早期胃癌再発時期別再発形式

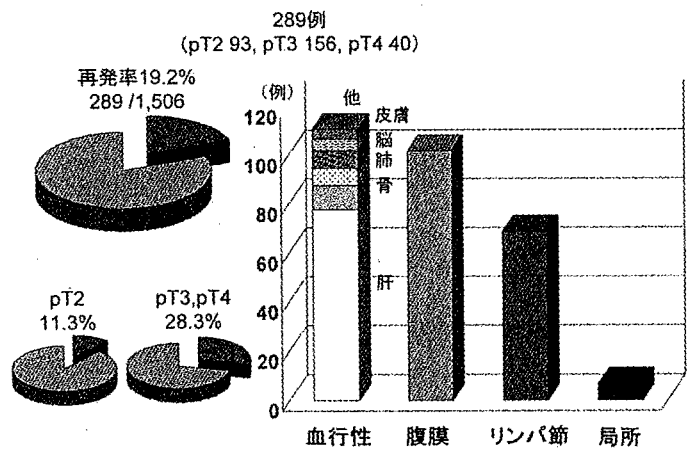

図 3 進行癌の再発状況

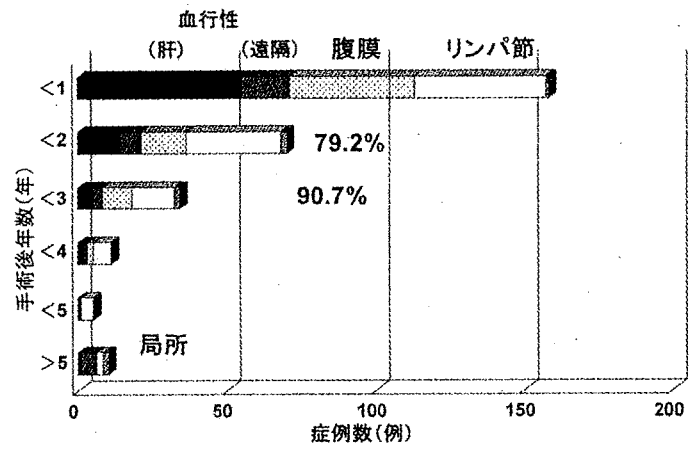

図 4 進行癌再発時期別再発形式

(181/806) で，腹膜再発が最も多く，血行性再発，リンパ節再発，局所再発の順であった。深達度別では pT2 で血行性再発が 2/3 を占め，腹膜再発は 10%もないが，pT3 になると腹膜再発が急速に増加し 42.8%を占め，pT4 では 64%が腹膜再発であった。

2）再発時期

術後 1 年以内再発例が最も多かったが，術後 2 年以内に 79.2%，3 年以内に 90.7%が再発していた (図 4)。術後 5 年以降の再発は 3.5%と少なかった。

3）遠隔成績

各再発形式別の術後 50%生存期間 (MST) と 3 年生存率はそれぞれ血行性再発 642 日，28.0%，腹膜再発 787 日，23.5%，リンパ節再発 650 日，26.1%，局所再発 1,067 日，42.9%であった (図 5)。また，再発後の MST と 3 年生存率はそれぞれ血行性再発 240 日，7.4%，腹膜再発 193 日，6.2%，リンパ節再発 277 日，19.8%であり，

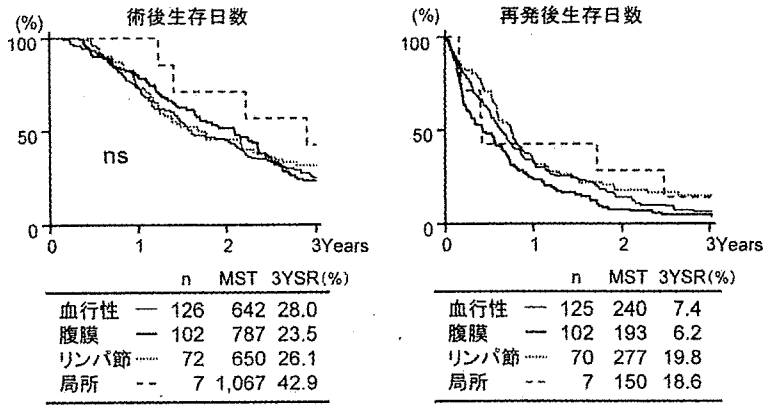

図 5　再発形式別遠隔成績

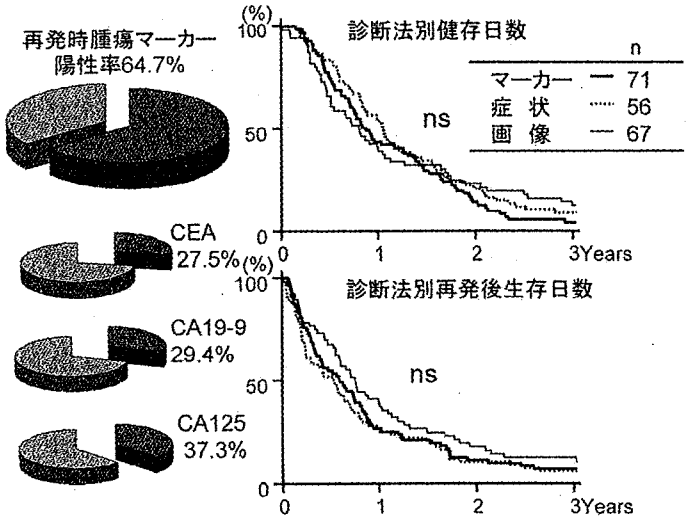

図 6　腹膜再発例における再発時腫瘍マーカーと診断法別遠隔成績

3大再発形式の術後および再発後の遠隔成績には差がなかった。局所再発は症例数が少ないものの術後生存日数は他の再発形式に比べやや長いが，再発後生存日数の延長は認められなかった。

腹膜再発例の腫瘍マーカー（CEA，CA19-9，CA125）推移と診断方法別遠隔成績についてみると（図6），腹膜再発時の腫瘍マーカー陽性率は64.7%であり，CEA 27.5%，CA19-9 29.4%，CA125 37.3%であった。腹膜再発例の診断方法別術後健存率，および再発後生存率は図6に示すごとく，腫瘍マーカー上昇による診断例，症状による診断例，画像診断例との間にほとんど差が認められなかった。

4．フォローアップ計画に必要なその他の諸因子

胃癌術後の早期においては，胃切除後症候群に対する観察・治療や食事指導をはじめとする生活指導が重要である。

近年，胃癌患者が高齢化してきているためか多発胃癌が増加しており，多発胃癌を念頭においた質の高い観察が望まれる。早期胃癌においては術後長期生存する可能性が高いため，初回手術時の見逃し病変や診断不能病変を経過観察中に指摘し，残胃癌を治療することにより治癒できる可能性が高い。また，早期胃癌術後は残胃に新生してきた胃癌に対しても治療効果が十分に期待できる。

他臓器癌に関しては二次発癌で発生頻度の高い部位は，男性では肺，大腸，肝，前立腺，食道などであり，女性では乳房，大腸，子宮，肺，胆嚢，肝などである。しかし，これらは基本検診，会社検診や人間ドックなどによりカバーする方針とした。

一方，Stage Ⅳなどの非治癒切除胃癌や再発胃癌に対する治療指針はいまだ定まっておらず，今回はフォローアップ計画を立てることを断念した。

5．術後のフォローアップ計画

早期胃癌が主体であるStage ⅠA，Stage ⅠBと治癒切除可能な進行胃癌が主体であるStage Ⅱ，Stage ⅢA，Stage ⅢBに対し，今後は地域連携も盛んになってくる

表 2 Stage Ⅰフォローアップ計画

術後（年）	1M	6M	1Y	1Y 6M	2Y	2Y 6M	3Y	4Y	5Y	6Y	7Y	8Y	9Y	10Y
問診・診察，PS，体重	○	○	○	○	○	○	○	○	○	○	○	○	○	○
検査（末梢血，生化学，TM）	○	○	○	○	○	○	○	○	○	○	○	○	○	○
US				○		○								
CT			○		○		○	○	○					
Chest X-P			○				○		○					
GTF			○				○		○		(○)			○

*必要時に施行：残胃造影，注腸，CF，骨シンチ，PET
*5年後以降は基本健診，職場検診や人間ドックを有効利用する

表 3 Stage Ⅱ～ⅢB フォローアップ計画

術後（年）	2W	3M	6M	9M	1Y	3M	6M	9M	2Y	6M	3Y	6M	4Y	6M	5Y
問診・診察，PS，体重	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
検査（末梢血，生化学，TM）	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
US							○			○		○			
CT					○				○		○		○		○
Chest X-P					○						○				○
GTF					○						○				○
補助化学療法（S-1）															

*必要時に施行：残胃造影，注腸，CF，骨シンチ，PET
*5年後以降は基本健診，職場検診や人間ドックを勧める
TM（CEA，CA19-9，CA125）

ことを考慮して術後フォローアップ計画を作成した。定期的な胃切除後フォローアップ計画の実際を示す。

1）Stage Ⅰ胃癌術後フォローアップ計画（表2）

外来受診時は問診，診察，血液生化学的検査や腫瘍マーカーのチェックを行う。腫瘍マーカーはCEA，CA19-9が主体である。画像診断ではUS，CT，上部内視鏡，胸部X線を必須とし，残胃透視，注腸，CF，骨シンチ，PETなどは必要時に施行することとした。術後1か月目に外来受診し，以後3年までは6か月ごとの受診とする。以後は1年ごとの受診とし10年まで観察する。早期胃癌は治癒する可能性が高く，今までも10年生存率によって他施設との比較がなされてきた経緯がある。また，残胃の癌，内視鏡治療後遺残例・再発例や高齢者増加による他病死の実態を把握するためにも10年後の成績把握を考慮した。

2）Stage Ⅱ/Ⅲ胃癌術後フォローアップ計画（表3）

ACTS-GCの結果[7]を踏まえて胃癌治療ガイドラインにも術後1年間はS-1を服用することが標準治療と指定されたため，4週投与2週休薬を原則として8コース施行することになり，少なくとも6週間ごとには外来受診することになる。外来受診時は問診，診察，血液生化学的検査や腫瘍マーカー（CA125を追加し，AFP産生胃癌ではAFPを追加）のチェックを行う。視診，触診にも力を入れ，頸部リンパ節の触診，貧血・黄疸の有無，腹部触診，直腸診などを行い，必ず体重も測定する。画像診断はStage 1と同様にUS，CT，上部内視鏡，胸部X線を必須とし，残胃透視，注腸，CF，骨シンチ，PETは必要時に施行することとした。術後2年までは3か月ごとに受診していただき，術後3年から5年までは6か月ごとの受診とした。定期的な術後フォローアップはここで終了とし，5年以降はかかりつけ医に依頼するか，基本検診，会社検診や人間ドックを毎年受けるように勧める。なお，胃全摘後の大球性巨赤芽球性貧血に対しては半永久的に6～12か月ごとにビタミンB_{12}の補給が必要となる。

Ⅲ．考　察

諸家の報告では腹膜播種再発が最も多く[8,9]，当科との乖離がみられる。その理由として，当科では腹膜播種が疑われる症例に対し積極的に術前審査腹腔鏡を施行しており，腹膜播種陽性例が適格に対象から除かれていることや血行性再発が定期検査で初発再発像として診断しやすく，腹膜再発の早期診断が困難であることを反映したものと考えている。胃癌術後定期的なフォローアップにより再発後の生存期間は改善されているのであろうか。無症状で再発が発見された場合は，有症状で発見された