the rho-shaped intestine, and the outlet from the stomach flows in two directions, preventing DGE. However, the usefulness of this reconstruction method has not been established, because there has not been a prospective study to evaluate the method. Therefore, we conducted a randomized controlled trial (RCT) comparing rRY and conventional RY reconstruction after distal gastrectomy.

The aim of the present study was to prospectively evaluate the frequency of DGE in patients who had undergone distal gastrectomy for gastric malignant disease, in comparison with conventional RY and rRY reconstructions.

Patients and methods

Eligibility criteria

Between May 2004 and October 2006, 70 patients with gastric cancer cared for in Osaka National Hospital were enrolled. Disease staging was performed according to the guidelines for clinical and pathologic studies on gastric cancer of the 13th edition of the Japanese Classification of Gastric Carcinoma [12]. Patients who required distal gastrectomy for gastric cancer with reconstruction other than BI were eligible for this study. Other eligibility criteria were age between 20 and 90 years; Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; RY reconstruction after resection required; acceptable renal and hepatic function, and normal electrocardiogram (ECG). Patients were excluded if they had active infection, severe heart disease, pregnancy, active synchronous carcinoma, interstitial pneumonia or pulmonary fibrosis, carcinoma of the remnant stomach, Borrmann type 4 disease (linitis plastica), or noncurative conditions such as peritoneal dissemination, hepatic metastasis, or severe invasion of other organs at preoperative diagnosis. A patient with an anamnesis of laparotomy for upper gastrointestinal diseases was also excluded. Written informed consent from all patients and the approval of the Institutional Review Board were obtained. This protocol was registered in a suitable electronic and freely accessible registry (UMIN-CTR ID # 960).

Randomization and statistical analyses

The primary endpoint was the frequency of DGE after operation, and secondary endpoints were the length of postoperative hospital stay, postoperative complications, and nutritional status after operation. Because the likelihood of DGE was nearly in proportion to T stage, patients were randomly assigned intraoperatively to undergo either standard + conventional RY reconstruction (RY group) or rRY reconstruction (rRY group) performed with the minimization method, according to T stage (sT1 versus sT2–3), age (below 70 years versus above 70 years), and body mass index (below 25 versus above 25). Nutritional status after gastrectomy has generally been believed to be affected by various factors, such as age and body mass index.

Intraoperatively, the surgeon was informed of the randomization arm immediately, and then completed the operation according to the established protocol. The postoperative course and dietary schedules were regulated in a clinical pathway in our institute. Patients were diagnosed with DGE based on the criteria [7, 13] that postoperative oral feeding was prohibited because of postprandial pain, nausea, or vomiting and the postoperative hospital stay was longer than 21 days. We determined the time of patient discharge according to the "discharge criteria" in a clinical pathway. These criteria were defined by (1) absence of fever over 37°C and (2) capacity to eat half of the daily regular solid diet. Abdominal x-ray, upper gastrointestinal (GI) series, and endoscopic examinations were performed to rule out possible causes of clinical symptoms other than DGE, such as remnant gastritis, anastomotic stricture, and intestinal obstruction. Thus DGE was defined as functional obstruction of the Roux limb, including RY stasis syndrome. The reported frequency of DGE after RY reconstruction is 15%, whereas that after BI was 4% (13) in our institution. Under the selection design of a randomized phase II trial, the sample size was estimated to be 70 (35 in each group) to select the better reconstruction method with probability of 90%, based on the expectation that a 10% difference will be observed in the frequency of DGE between the two groups. This protocol followed the nutritional status assessed by body weight and serum albumin for one year following surgery. Mann-Whitney *U*-test and chi-square test were used for the analysis where appropriate to assess differences between groups. Univariate and multivariate analyses were performed by using logistic regression analysis adjusting the baseline confounding factors. All statistical analyses were performed with SPSS software version 15.0 J. Two-sided *P* values were calculated and presented. A P value <0.05 was considered to indicate statistical significance.

Operative procedure

Endotracheal anesthesia and a standard midline laparotomy incision were used for all patients in our institution. Gastric tumors located in the lower third or the lower two-thirds of the stomach were treated by distal or subtotal gastrectomy. For D1–2 lymphadenectomy as defined in the Japanese Classification for Standard Dissection [12], D1 meant dissecting paragastric nodes, and D2 involved dissection of the nodes along the left gastric artery, the nodes along the

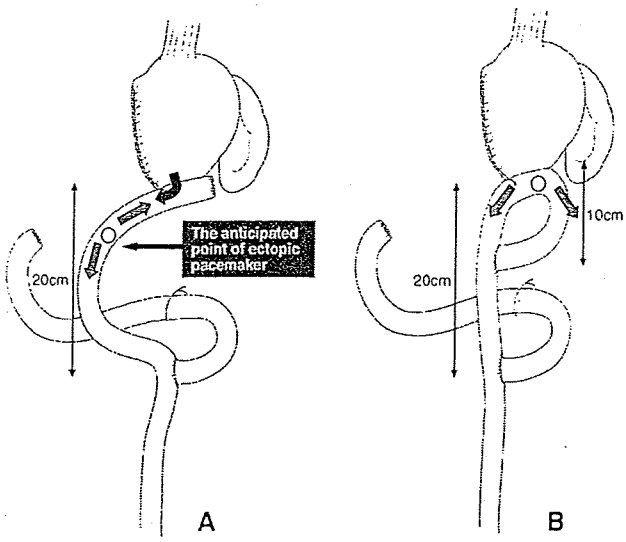

Fig. 1 Scheme of the conventional RY reconstruction (a) and rho-shaped RY reconstruction (b)

common hepatic artery, and the nodes around the celiac artery in addition to D1 lymphadenectomy. D3 lymphadenectomy meant dissection of the hepatoduodenal nodes, retropancreatic nodes, those along the superior mesenteric vein, and the para-aortic nodes between the level of the celiac axis and the inferior mesenteric artery, all in addition to standard D2 lymphadenectomy.

For conventional RY gastrojejunostomy, the jejunum was divided 20 cm distal to the ligament of Treitz, and the portion of the jejunum closest to the patient's head was closed in two layers, followed by the remaining gastric pouch, which was anastomosed retrocolically to the jejunum about 2 cm distal to the closed site by an end-to-side procedure. The orad portion of the jejunum was then anastomosed to the mid-jejunum 20 cm distal to the gastrojejunostomy. For the rRY reconstruction, rho-shaped jejunum 30 cm long was prepared and the remaining gastric pouch was anastomosed to the top of the rho shape, with the orad portion of the jejunum anastomosed to the mid-jejunum 20 cm distal to the gastrojejunostomy (Fig. 1). Uniformly, the anastomoses were done by hand sutures.

Results

Recruitment commenced in May 2004 and was concluded in October 2006. A total of 70 adult patients (45 men and 25 women) with gastric adenocarcinoma who underwent distal gastrectomy at Osaka National Hospital were enrolled: 35 in RY group and 35 in rRY group. A total of 44 patients had stage I disease, 6 stage II, 14 stage III, and 6 stage IV disease. A D1 lymphadenectomy was performed in 1 patient, with D2 done in 58 patients, and D3 in 11 patients. Patient characteristics were well balanced between the two groups (Table 1). Because one patient in the rRY group was mistakenly assigned to the RY group intraoperatively, he was included in that group based on the intention-to-treat principle (Fig. 2).

Table 1 Patient characteristics

Variables	RY group ($n = 35$)	rRY group ($n = 35$)	P value
Age (years)			0.52
Median (range)	64 (28–82)	65 (41–90)	
Sex. no. (%)			0.32
Male	20 (57)	25 (71)	
Female	15 (43)	10 (29)	
Body mass index			1.00
<25.0	30 (86%)	30 (86%)	
≥25.0	5 (14%)	5 (14%)	
Surgical TNM stage			0.79
I or II	26 (74%)	24 (69%)	
III or IV	9 (26%)	11 (31%)	
Preservation of vagal trunks. no. (%)			1.00
Yes	13 (37)	12 (34)	
No	22 (63)	23 (66)	

RY Roux-en-Y; *rRY* rho-shaped Roux-en-Y reconstruction

The overall operative morbidity rate was 14% (Table 2). The blood loss for the rRY group patients was more than for the RY group (260 ml and 150 ml, respectively), but the difference did not reach statistical significance ($p = 0.06$). Operative time and postoperative hospital stay showed no significant differences between the two groups. Postoperative hospital death did not occur in either group. No patients in this study had the dumping syndrome or severe esophageal reflux after operation (data not shown).

The relative body weight, at one year after surgery, was 90% for the RY group and 91% for the rRY group. The serum albumin level was not changed, even one year after surgery (99% for both groups). There were no statistically significant changes in the relative body weight ($P = 0.40$) and serum albumin ($P = 0.90$) between the two groups.

Postoperatively DGE occurred in two patients (6%) after the RY operation, and four patients (11%) after rRY reconstruction ($P = 0.67$) (Table 3). We routinely administered the motility agent erythromycin lactobionate (1,000–1,200 mg/day, oral or intravenous administration), to patients who had DGE postoperatively for 1–2 weeks. All 6 patients who had DGE after operation were discharged within 34 days from the hospital without symptoms. The interval from the day when oral feeding was stopped until the day it was restarted was 2 to 12 days. On average, the postoperative day (POD) on which DGE occurred and oral feeding was stopped was POD 10 (range:

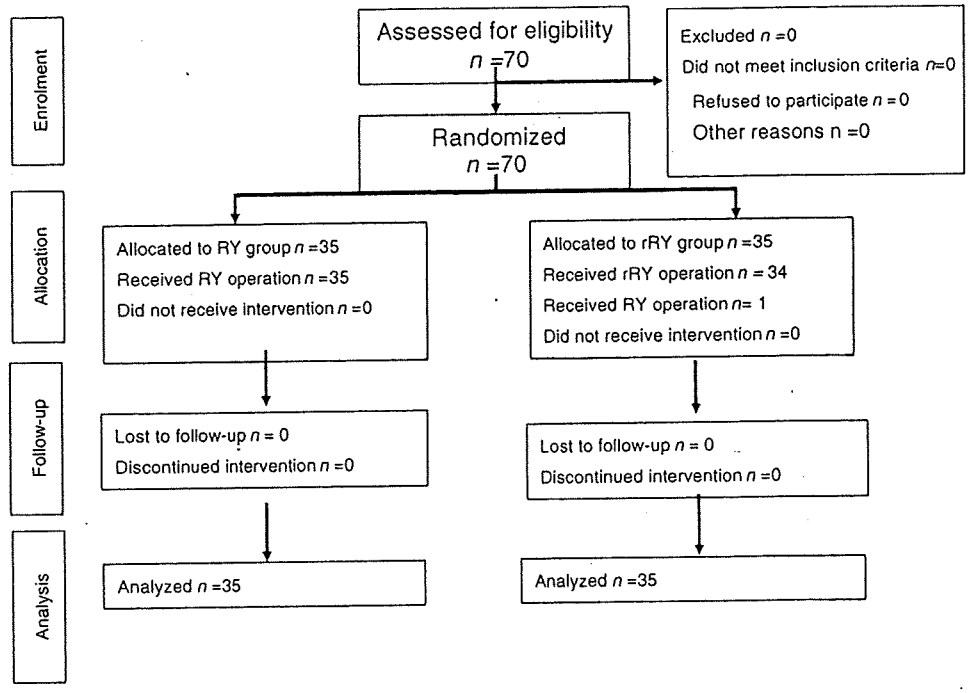

Fig. 2 CONSORT flow chart [27]

Table 2 Surgical outcomes and morbidities

Variables	RY group (n = 35)	rRY group (n = 35)	P value
Blood loss, ml			0.06
Median (range)	150 (70–1100)	260 (30–1070)	
Operative time, min			0.64
Median (range)	214 (136–349)	219 (146–295)	
Postoperative hospital stay, days			0.34
Median (range)	14 (9–81)	14 (10–46)	
Any complication, no. (%)	5 (14)	5 (14)	1.00
Abdomincal abscess	2 (6)	4 (11)	0.67
Bleeding	1 (3)	1 (3)	1.00
Pancreatic fistula	1 (3)	0 (0)	1.00
Bile fistula	1 (3)	0 (0)	1.00
Mortality, no. (%)	0 (0)	0 (0)	1.00

6–14 days) in the RY group and POD 13 (4–19 days) in the rRY group (Table 3).

We analyzed the predictive factors of DGE occurrence with univariate and multivariate analyses (Table 4). When assessed by univariate analysis, preservation of the vagal trunk entering the celiac axis statistically significantly increased the risk of DGE occurrence. Multivariate analysis identified that preservation of vagal nerves was the only significant predictor of DGE occurrence, and the odds ratio was 23.5 (95% confidence intervals, 1.74–316.8).

Discussion

Gastric surgery may potentiate or induce DGE and result in chronic gastroparesis [14]. Two major hypotheses have been proposed and reported to explain functional DGE or Roux stasis syndrome [7]. According to the first hypothesis, the gastric remnant produces acid that passes into the Roux limb and disturbs its motility. The acid is probably poorly buffered by alkaline secretion in the proximal part of the Roux limb. The second hypothesis is that the Roux limb itself causes functional obstruction of the gastric outlet. Miedema and Kelly [9] found that separation of the Roux limb from the duodenal pacemaker [15] by jejunal transection allowed the ectopic pacemakers to arise in the Roux limb and drive contractions orad.

Because the changes in gastric emptying after the various forms of vagotomy, drainage procedures, gastric resection, and the several methods of gastrointestinal reconstruction have been discussed elsewhere [16], we confine our discussion here to the increased postoperative risk of DGE in predisposed individuals. Patients with obstructive ulcer disease have been reported to be at increased risk of postoperative gastric atony [17]. The prevalence of DGE after gastrectomy has been reported to range from 5% to 30% [5–7, 18]. Delayed gastric emptying has also been reported to continue to affect a considerable number of patients (24%) after gastric surgery, and to be particularly common in patients with diabetes, malnutrition, and gastric or pancreatic cancer [18]. Moreover, it has been reported that RY reconstruction after gastric cancer

Table 3 Characteristics of the patients with DGE following operations

Group	Age	Sex	BMI	sStage	Presv nerves	POD stopped	Interval	POH stay
RY	67	Male	24.5	IA	Yes	14	9	30
RY	67	Male	26.7	IA	Yes	6	12	22
rRY	75	Male	24.6	IA	No	4	8	32
rRY	69	Male	24.2	IA	Yes	14	2	24
rRY	74	Male	22.8	IA	Yes	12	3	30
rRY	67	Male	21.4	IA	Yes	19	2	34

DGE delayed gastric emptying, *BMI* body mass index, *sStage* surgical TNM stage, *Presv nerves* preservation of vagal trunks, *POD stopped* postoperative day when oral feeding was stopped, *Interval* interval from the day when oral feeding was stopped until the day it was restarted (days), *POH stay* postoperative hospital stay

Table 4 Association between clinical and surgical factors and DGE occurrence

Factors	Category	Univariate		Multivariate	
		Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Age		1.06 (0.97–1.16)	0.19	1.13 (0.99–1.29)	0.08
Sex	Male	NE	1.00	–	–
BMI	≥25.0	1.22 (0.13–11.7)	0.86	1.70 (0.14–21.3)	0.68
sStage	III or IV	NE	1.00	–	–
Presv nerve	Yes	11.0 (1.21–100.4)	0.03	23.5 (1.74–316.8)	0.02

NE, not able to estimate

resection causes DGE significantly more often than BI reconstruction after gastrectomy for gastric carcinoma [13].

Delayed gastric emptying occurring in the early postoperative period is generally thought to resolve spontaneously within 6 weeks of surgery, and the temptation to reoperate on a nonobstructed stomach should therefore be avoided [14, 17]. Various prokinetic agents have been tested as means of enhancing gastric emptying of solids after RY reconstruction, including bethanechol chloride [19], metoclopramide [18, 20], cisapride [21], ondansetron [22] (a potent 5-hydroxytryptamine-3 receptor antagonist), and erythromycin lactobionate [23] (as a motilin agonist), and may be useful agents in patients with stasis, although the long-term results of use of these agents is still unknown. In the present study, erythromycin lactobionate was administered after operation for about 1–2 weeks to all 6 patients who had DGE.

The uncut Roux-en-Y gastrojejunostomy has been reported to be an attractive alternative to distal gastrectomy, because ectopic pacemaker potentials and potential motor abnormalities in the Roux limb have been found to be suppressed with it, at least in dog and pig models [8, 9, 24, 25]. It was reported that the uncut Roux loop was less suitable for clinical use because of staple dehiscence. However, evidence of the clinical efficacy of the uncut Roux-en-Y gastrojejunostomy is lacking [26]. Other surgical methods such as rho-shaped RY reconstruction have been reported to be effective in preventing RY syndrome [10, 11]. Rho-shaped anastomosis after gastrectomy was previously reported to be feasible and useful by Ou-Uti et al. [11], who investigated rho-shaped jejunal passage after total gastrectomy using an elaborate barium meal examination. Moreover, the hypothesis that an ectopic pacemaker of the Roux limb is located at the top of the rho-shaped jejunum and that the outlet from stomach flows in two directions has been proposed to explain the effectiveness of rRY reconstruction in preventing RY stasis syndrome. In our study, however, postoperative DGE occurred in two patients (6%) after RY operation, and in four patients (11%) after rRY reconstruction ($p = 0.67$). Secondary endpoints, the length of postoperative stay, postoperative complications, and nutritional status after operation in some patients, also showed no significant differences between two groups. Although the rRY operation was considered to be a safe and feasible method, we could not see the advantage of rRY comparing to conventional RY method. Although the exact mechanism was unclear, the rho-shaped Roux limb of rRY reconstruction was considered to cause similar functional obstruction to that occurring after a conventional RY repair.

We additionally analyzed the predictive factors of DGE occurrence. We have previously reported that the DGE after RY operation for gastric cancer was more frequent among patients undergoing extensive lymph node dissection than among those receiving conventional dissection in the retrospective study [13]. This prospective study showed that lymph node dissection was not associated with the occurrence of DGE. Our study also showed that truncal vagotomy was associated with the inhibition of the RY DGE. It is difficult to explain these contradictory findings.

Preservation of the vagal trunk entering the celiac axis might change the location of the ectopic pacemaker point in the rho-shaped Roux limb, or it might drive the contractions of the proximal part of the limb in a reverse or orad direction toward the stomach in the early phase, 1–2 weeks after operation. According to the hypothesis noted above, the gastric remnant produces acid that passes into the RY limb and may disturb its motility. In this study, the remnant stomach, with preservation of the vagal trunk, might also have produced more acid than is produced in the early postoperative phase following surgery with vagotomy.

The limitation of our study was the small number (35 in each group) of patients. The negative results of our study may result from the study design with low power due to small number of patients. Furthermore, this study was conducted in a non-blinded fashion, because surgical RCT has various difficulties for blinding to patients or doctors. However, the DGE occurrence in rRY was twice as high as that in RY, suggesting that the possible superiority of rRY is low, even if we conducted a large RCT in a blinded fashion.

This RCT was conducted in one hospital where about 200 gastrectomies are performed annually. It is well known that single-institutional RCTs have an issue regarding the generalizability of the results; however, a RCT comparing surgical methods has the additional issue of quality control of surgical techniques. On this point, our study has the advantage of homogeneity, because all surgeries were performed by three surgeons (M.H., K.F., and T.T.) with sufficient experience of gastric surgery.

To our knowledge, this is the first RCT report in the world concerning the occurrence of DGE following gastric surgery. Our findings show that DGE occurred to a similar extent and that operative morbidity and nutritional status after operation did not significantly differ between the RY and rRY groups. Our findings suggest that RY reconstruction after distal gastrectomy may be as simple and effective as conventional reconstruction.

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Feasibility Study of S-1 plus Weekly Docetaxel Combined with Concurrent Radiotherapy in Advanced Gastric Cancer Refractory to First-line Chemotherapy

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Abstract. *Background: As there is no standard treatment for advanced gastric cancer refractory to first-line chemotherapy, the feasibility of S-1 plus weekly docetaxel combined with concurrent radiotherapy was evaluated. Patients and Methods: Ten patients were enrolled in this study. Patients were given S-1 at a daily dose of 40 mg/m^2 and docetaxel at a weekly dose of 20 mg/m^2 for 5 consecutive weeks, with concurrent radiotherapy (RT) amounting to a total irradiation dose of 45 Gy or 50.4 Gy. Results: Hematological toxicities were grade 3 or less except for anemia. Non-hematological toxicities were all grade 2 or less, apart from one grade 3 asthenia. There was one treatment-related death, resulting from melena, in a patient with a mechanical device in the radiation field. Planned treatment was delivered with relative dose intensity for S-1, docetaxel and RT as 94%, 98% and 97%, respectively. Median survival time of 297 days was obtained, with an objective response seen in 2 patients and symptom relief achieved in all patients. Conclusion: S-1 plus weekly docetaxel combined with concurrent RT exhibited a tolerable toxicity profile with sufficient symptom palliation and prolonged survival in patients with advanced gastric cancer refractory to first-line chemotherapy.*

Surgical resection remains the mainstay for curative treatment of advanced gastric cancer (AGC). However, even when a complete resection can be achieved, postoperative recurrence may occur. Once the disease relapses, it seems lethal. Treatment mainstream for the recurrent disease is chemotherapy. Various chemotherapy regimens have been studied in patients with AGC. Although a median survival time (MST) of 6-11 months has been obtained (1-6), the therapeutic impact of these results on survival is considered to be modest and there has been no generally accepted standard regimen for the treatment of AGC so far. However, S-1 (an oral fluoropyrimidine) plus cisplatin has recently shown an MST of 13 months in a phase III trial and holds promise of becoming a standard first-line treatment for AGC (7). Contrary to these developments in first-line chemotherapy for AGC, standard regimen for second-line therapy still remains unclear as there have been no randomized phase III studies.

As for radiotherapy (RT), another treatment modality for AGC, several studies have shown the efficacy of RT against AGC concurrently used with chemotherapy either preoperatively (8-11) or postoperatively (12). High pathological complete response (pCR) rates of 20% to 30% and good local control obtained by chemoradiotherapy (CRT) suggest that CRT could also be a candidate for post first-line therapy in patients with AGC.

Although infusional 5-fluorouracil (5-FU) has been used most commonly with RT because of its radiosensitizing property (8-12), other agents such as cisplatin (11) and paclitaxel (9, 10) have also been used in combination with 5-FU. There has been no generally accepted standard chemotherapy regimen combined with RT against AGC.

S-1 is an active agent against AGC (13), composed of tegafur (1-(2-tetrahydrofuryl)-5-fluorouracil; FT) and two modulating agents, 5-chloro-2,4-dihydroxypyridine (CDHP) and potassium oxonate (Oxo), at a molar ratio of 1:0.4:1 (14). FT is converted primarily in the liver to 5-FU, a conventional radiosensitizer. CDHP is a reversible competitive inhibitor of dihydropyrimidine dehydrogenase (DPD) which degrades 5-FU, and is also known to have a radiosensitizing property. Therefore, S-1 can be anticipated as a suitable agent for CRT against AGC because of its radiosensitizing properties as well as its cytotoxic activity. Recently, synergism of S-1 with RT has been confirmed in human cancer xenografts (15, 16).

Docetaxel, another active agent for AGC, has also been identified clinically as an effective radiosensitizer in various types of cancer with weekly dosing (17, 18). Docetaxel

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Key Words: Feasibility study, S-1, weekly docetaxel, concurrent radiotherapy, advanced gastric cancer.

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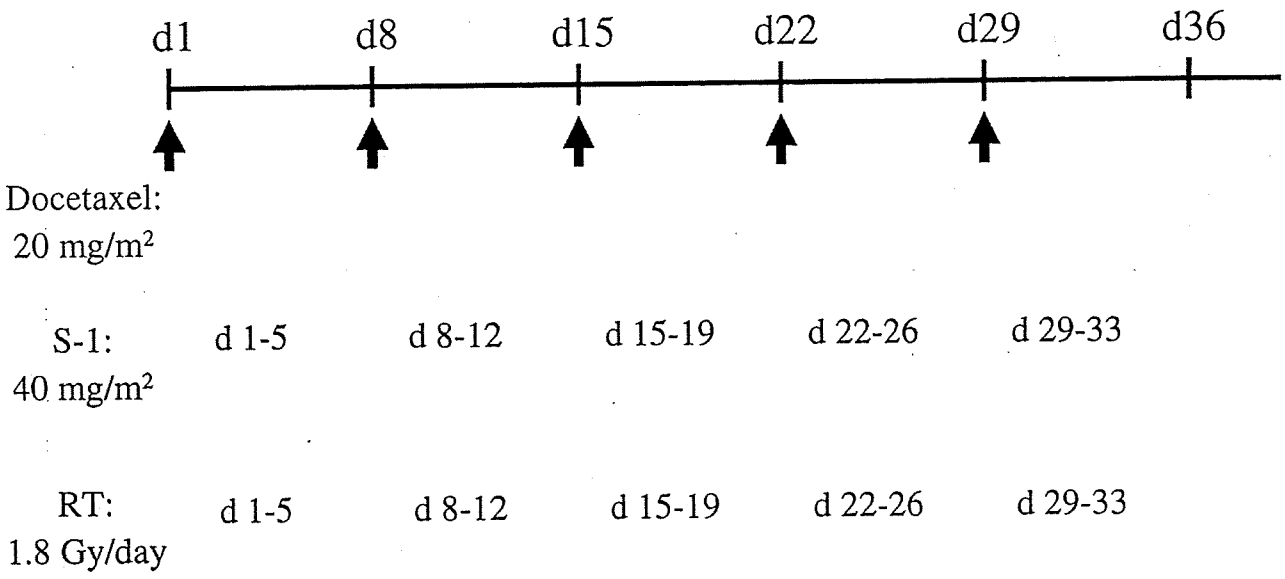

Figure 1. *Treatment schedule. RT, radiotherapy.*

synchronizes the cell cycle to the G_2/M-phase, which is the most vulnerable period for radiation (19), and shows synergistic cytotoxicity with RT in various human cancer cell lines *in vitro* (20, 21).

Anticipating radiosensitizing effects as well as tumoricidal effects by S-1 and docetaxel, we conducted the present feasibility study of CRT employing S-1 and weekly docetaxel in patients with AGC refractory to first-line chemotherapy.

Patients and Methods

Eligibility criteria. Tumor assessment was performed within 4 weeks before entry, and a complete blood cell count, liver and renal function tests were carried out within 2 weeks prior to entry. Patients enrolled in this study were required to fulfill the following criteria: (i) histologically proven unresectable or recurrent GC with measurable lesions, (ii) performance status of 1 or less on the Eastern Cooperative Oncology Group (ECOG) scale, (iii) life expectancy of at least 3 months, (iv) age of 80 years or younger, (v) at least one prior chemotherapy for the disease before entry, (vi) no prior radiation therapy, (vii) adequate bone marrow function (WBC count 3,000-12,000/mm^3, platelet count ≥100,000/mm^3, and hemoglobin ≥8.0 g/dl), hepatic function (total bilirubin ≤2.0 mg/dl, serum transaminases ≤3.0 x upper institutional limit), and renal function (serum creatinine ≤1.5 mg/dl), (viii) tolerance of oral feeding, (ix) no other severe medical conditions, (x) no other concurrent active malignancy, and (xi) provision of written informed consent.

Treatment schedule. The treatment schedule is illustrated in Figure 1. S-1 was given orally twice daily after meals at a dose of 40 mg/m^2/day every Monday through Friday for 5 consecutive weeks. The dose of S-1 was assigned according to the body surface area (BSA) of the patient as follows: BSA<1.25 m^2, 40 mg/day; 1.25 m^2≤ BSA<1.5 m^2, 50 mg/day; and BSA≥1.5 m^2, 60 mg/day. Docetaxel was administered intravenously at a dose of 20 mg/m^2 over 60 minutes before irradiation with a standard antiemetic prophylaxis every Monday for 5 consecutive weeks. Radiotherapy was also delivered concurrently with chemotherapy every Monday through Friday for 5 consecutive weeks. A total irradiation dose of 45 Gy was delivered in 25 fractions of 1.8 Gy over 5 weeks to the former 5 patients and 50.4 Gy in 28 fractions of 1.8 Gy over 5.5 weeks to the latter 5 patients, consequtively.

Chemotherapy was continued if the biological parameters still conformed to the eligibility criteria, except for the leukocyte count (≥2,000/mm^3) and the platelet count (≥75,000/mm^3). When the patient developed non-hematological toxicity of grade 3 or more, chemotherapy was suspended.

Radiation fields encompassed the tumor with a 2-cm margin. The fields were modified as needed to shield at least two-thirds of one kidney. Linear accelerators delivered the radiation dosage using 10-MV photons and, if necessary, a three-dimensional conformal technique was used to spare the heart, lungs and spinal cord, and to minimize the radiation dose to the small bowel and liver. While undergoing RT, patients were evaluated weekly by a radiation oncologist. The RT schedule was interrupted if the patient developed grade 4 leukopenia, neutropenia, and/or thrombocytopenia.

Granulocyte colony-stimulating factor (G-CSF) was used when grade 4 leukopenia and/or neutropenia were observed. The treatment was continued unless disease progression or intolerable toxicity occurred.

Evaluation of toxicity and efficacy. A complete blood cell count and measurements of liver and renal function were assessed at least every week during the treatment. Non-hematological toxicities were also verified at least every week by patient interview and physical examination. Toxicity was graded according to the National Cancer Institute (NCI) common toxicity criteria version 3.0.

Within 4 weeks after the completion of CRT, patients were evaluated with abdominal computed tomography (CT) scans and assessed for locoregional control according to the RECIST criteria. A

Table I. *Patient characteristics.*

Patient no.	Gender	Age (years)	PS	Prior Gx	T, N stage	Histology	Prior chemotherapy	Target tumor	RT dose (Gy)
1	M	68	1	Total	T2N3	Intestinal	S1/CPT, TXL	Lymph node	45
2	F	74	1	Total	T4N1	Diffuse	S1/CDDP	Local	45
3	M	57	1	Distal	T3N1	Intestinal	S1/CPT	Lymph node	45
4	M	71	1	Total	T3N1	Diffuse	S1, CPT/CDDP, TXL	Lymph node	45
5	M	57	1	(–)	T3N2	Diffuse	S1/CDDP/TXL, S1/CDDP	Local	45
6	M	69	0	Distal	T2N3	Intestinal	S1/CDDP, S1/CPT	Lymph node	50.4
7	M	67	1	Total	T3N1	Diffuse	S1	Local	50.4
8	F	76	1	Distal	T3N2	Diffuse	S1	Lymph node	36*
9	M	71	0	Total	T3N3	Intestinal	S1/CDDP, CPT/CDDP, TXL,TXT	Lymph node	50.4
10	M	75	1	(–)	T3N1	Diffuse	S1/CPT, S1/CDDP	Lymph node	50.4

M, Male; F, female; PS, performance status; Gx, gastrectomy; CPT, irinotecan; TXL, paclitaxel; CDDP, cisplatin; TXT, docetaxel; RT, radiotherapy. Asterisk indicates the case of treatment-related death (TRD), in whom RT was discontinued at the dose of 36 Gy.

complete response (CR) was defined as complete disappearance of the tumor by CT scan. A partial response (PR) was defined as shrinkage in ≥30% of the tumor diameter. An increase in ≥20% of the tumor diameter, or the appearance of new lesions, was defined as progressive disease (PD). Stable disease (SD) was defined as not qualifying as a CR, PR or PD. Patients were also assessed for symptom relief.

Overall survival (OS) time since the initiation of CRT to the date of death of any cause or confirmed survival was recorded, and the Kaplan-Meier method was used to draw the survival curve. Patients who were alive at the time of our analysis were censored for survival.

Results

Patient characteristics. The clinical characteristics of the patients are shown in Table I. Ten patients, 8 males and 2 females with a median age of 70.0 years (range: 57-76), entered this single-center study between October 2006 and October 2008. All the patients had a performance status of 0 or 1. Five patients had previously undergone total gastrectomy and 3 had distal gastrectomy, while two patients had no gastrectomy because of the presence of distant metastasis (M1). T stage of the primary tumor was T2 in 2 patients, T3 in 7, and T4 in 1. N stage of the primary tumor was N1 in 5 patients, N2 in 2, and N3 in 3. Histologically, 4 patients had intestinal-type adenocarcinoma and 6 patients had diffuse-type adenocarcinoma. Prior chemotherapy had been given in all patients, with 1 regimen in 4 patients, 2 regimens in 4 patients, 3 regimens in 1 patient, and 4 regimens in 1 patient. As a target tumor of RT, lymph node relapse was observed in 6 patients and local recurrence in 2 patients after prior gastrectomy, while 2 patients with M1 disease had primary tumor and lymph node, respectively.

Toxicity. All the patients were assessable for toxicity. Table II lists all adverse events. Hematological toxicities were grade 3 or less in all the patients but one. A 76-year-old female developed grade 4 anemia accompanied by melena and grade 2 thrombocytopenia, resulting in treatment-related death (TRD) immediately after the discontinuation of the treatment despite hospitalization and blood transfusion. Non-hematological toxicities were all grade 2 or less, apart from grade 3 asthenia observed in one patient who had chemotherapy withheld for the last three days during the treatment. No patient suffered from febrile neutropenia of grade 3 or more, neuropathy of any grade or radiation dermatitis over grade 2.

Table II. *Toxicities recorded during the study.*

	NCI-CTC Grade (n)			
	1	2	3	4
Leukopenia	2	2	2	
Neutropenia	2	4	1	
Anemia	5	0	3	1*
Thrombocytopenia	2	1*		
Stomatitis	2			
Diarrhea	2	1		
Anorexia	4	1		
Nausea	5			
Vomiting	1			
Asthenia	7	1	1	
T-bil		1		
AST/ALT		1		

Asterisk indicates the case of treatment-related death (TRD).

S-1 administration was skipped in 4 patients: for 3 days in 2 and for 5 days in 2, due to grade 3 leukopenia in 2, grade 3 asthenia in 1, and TRD in 1, respectively. Docetaxel was delivered as scheduled in all the patients but one, who

Table III. *Clinical efficacy.*

Patient no.	Response	Presenting symptom	Symptom relief	Alive/Dead
1	PR	Pain	Disappeared	D
2	SD	Pain and dysphagia	Improved	D
3	PR	None		D
4	SD	None		D
5	SD	Dysphagia	Improved	A
6	SD	None		A
7	SD	Dysphagia	Improved	D
8	SD	Obstructive jaundice with PTCD		D (treatment-related)
9	SD	None		D
10	SD	None		D

PR, partial response; SD, stable disease; PTCD, percutaneous transhepatic cholangiodrainage.

could not receive the fifth weekly dose of docetaxel because of TRD during the treatment. Received dose intensity was 37.6 mg/m^2 per day for S-1 and 19.6 mg/m^2 per week for docetaxel, corresponding to a relative dose intensity of 94% and 98%, respectively.

RT was conducted as scheduled in 9 out of 10 patients, excluding the case of TRD in whom RT was discontinued after reaching a dose of 36 Gy. The relative dose intensity of RT was 97%.

Clinical efficacy. The objective response to treatment is shown in Table III. A PR was achieved in 2 patients while the remaining 8 patients showed SD, yielding a disease control rate of 100%.

Just prior to the CRT, two patients with lymph node recurrence each complained of pain or obstructive jaundice. Of the other 3 patients presenting with dysphagia because of local relapse around the esophagojejunal anastomosis in 2 and primary tumor of the gastroesophageal junction in 1, one complained of pain as well. After the completion of CRT, pain disappeared in 1 and decreased in 1, respectively. Dysphagia improved in all 3 patients, greatly facilitating oral intake.

The MST of all patients after the commencement of CRT was 297 days, as shown in Figure 2. Seven patients died of disease progression, and one patient suffered from TRD. Additional chemotherapy was given after the completion of CRT in 5 out of 10 patients.

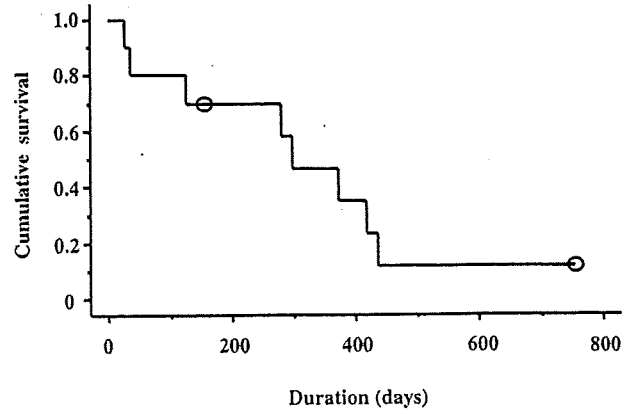

Figure 2. *Overall survival. Circles indicate the censored cases.*

Discussion

The first-line treatment for recurrent gastric cancer remains chemotherapy, despite the lack of a generally accepted standard regimen. Recent advances have yielded a prolonged MST of 13 months for AGC (7). Contrary to this development in first-line chemotherapy for AGC, the optimal modality for post first-line therapy is uncertain due to the lack of any randomized phase III studies. On the other hand, CRT has demonstrated superior local control against AGC when used preoperatively (8-10) and significant improvement in overall survival as adjuvant therapy (12). These findings lead us to a growing interest in CRT as a post first-line treatment in patients with recurrent gastric cancer.

Concurrent CRT commonly employs infusional 5-FU at a dose of around 300 mg/m^2 because of its radiosensitizing property (8-10). In this study, S-1, composed of tegafur and CDHP, was administered instead of infusional 5-FU because tegafur is converted to 5-FU and CDHP is also radiosensitizing. S-1 at a dose of 40 mg/m^2/day, the amount delivered in this study, is known to be equivalent to protracted venous infusion of 5-FU at a dose of 250 mg/m^2/day in terms of the area under the plasma concentration time curve (AUC) of 5-FU (22). In addition, S-1, being an oral fluoropyrimidine, can avoid the need for inconvenient and troublesome indwelling catheters and portable pump systems required for infusional 5-FU, which makes a striking

difference from conventional 5-FU-based regimens. Recently, S-1 plus low-dose cisplatin combined with RT has been reported to show a high response rate of 65% as an initial treatment for incurable or unresectable AGC (23).

Docetaxel is another potent radiosensitizer as well as being an active agent for AGC. Through its synchronization of the cell cycle to the G_2/M phase (19), docetaxel shows synergistic effect with RT on cancer cells (20, 21). When used concurrently with RT, docetaxel is usually administered on a weekly basis at a dose of 10-20 mg/m^2/week (17, 18). Weekly docetaxel is considered to inhibit progression of the tumor by shortening the interval between drug administration, and is known to show a better overall tolerability profile than 3-week dosing (24).

In anticipation of additive radiosensitizing effects as well as tumoricidal effects by both S-1 and docetaxel, we combined these two drugs with RT in patients with recurrent gastric cancer refractory to first-line chemotherapy.

The overall toxicity of this combination therapy was highly acceptable, as shown in Table II. Hematological toxicities were favorable except for grade 4 anemia which was related to a TRD. Non-hematological toxicities were also mild, apart from grade 3 asthenia observed in only one patient. In a recent phase II study of S-1 plus cisplatin combined with RT for AGC, the incidence of adverse reactions above grade 3 was 6.7% for anemia, 66.7% for leukopenia, 33.3% for thrombocytopenia, 6.7% for diarrhea, 23.3% for anorexia, 23.3% for nausea, and 6.7% for renal dysfunction, including 13.3% for grade 4 bone marrow toxicity (23). Likewise, a high incidence of grade 4 toxicities over 20% was reported when continuous infusion of 5-FU plus weekly paclitaxel was given concurrently with RT preoperatively (10). Although there are limitations to comparing different studies because of variations in the agents, dosage and schedule of chemotherapy, as well as the extent of prior treatment, the toxicity profile of this combination therapy seems highly acceptable compared with those reported in other studies. Such a low toxicity profile enabled the high relative dose intensity of chemotherapeutic agents and RT obtained in this combination therapy.

However, of note, one TRD was observed in this study. A 76-year-old female, who had a percutaneous transhepatic cholangiodrainage (PTCD) tube inserted in the radiation field because of obstructive jaundice due to lymph node recurrence, developed TRD accompanied by melena and grade 4 anemia. Although the origin of gastrointestinal (GI) bleeding was unknown because the patient received neither endoscopy nor angiography, RT might had been implicated as bleeding from the PTCD tube placed in the radiation field was observed. The incidence of GI complications associated with RT delivered to the right upper quadrant of abdomen has been reported to be 5.9% for gastric ulcer, 9.2% for duodenal ulcer, 5.9% for gastroduodenitis, 1.3% for perforation, 7.2% for bleeding, and 0.7% for fatal bleeding in patients with irradiated hepatocellular carcinoma (25). In addition, when delivering CRT, careful management of the patient is needed to monitor the safety of the treatment, especially in patients with mechanical devices present in the radiation field. As for the irradiated patients with esophageal stenting for advanced esophageal cancer, high morbidity rates are reported, including formation or worsening of esophageal fistulae (28%), massive hematemesis or GI bleeding (21%), and TRD (21%), with an overall grade 3-5 nonhematological toxicity rate of 51% (26). Considering the risk of life-threatening complications during RT, palliative intubation of mechanical devices in the radiation field might have to be delayed until CRT appears to have failed.

The objective response to treatment is shown in Table III. A PR was achieved in 2 patients, while the remaining 8 patients showed SD. Although high pathological CR rates of 13-26% as well as good response to CRT were observed when it was delivered as an initial treatment for AGC (10, 23), the response rate (RR) of 20% obtained in this study might be reasonable, given that all the patients had failed to respond to first-line chemotherapy. Significant correlations have been reported between the response to first-line chemotherapy and the response to subsequent CRT in patients with head and neck cancer and non-small cell lung cancer (27, 28). Generally, in patients with AGC refractory to first-line chemotherapy, objective response to second-line treatment is considered to be around 20% (29-31). In addition, it is of interest that an objective response to CRT was achieved only in patients with intestinal-type GC. The associations of intestinal-type GC with good response to CRT and better OS by CRT have already been reported elsewhere (12, 32).

Patients were also assessed for symptom relief. Satisfactory palliation of clinical symptoms such as pain and dysphagia was achieved in all patients. The three most frequent symptoms caused by AGC are pain, bleeding (hematemesis, melena), and obstruction (dysphagia, vomiting) (32, 33). These can have a significant impact on a patient's quality of life. RT has been used to alleviate these symptoms and control rates for pain, bleeding and obstruction have been reported to be 25-86%, 54-70% and 25-81%, respectively (32, 33).

The MST of all patients recruited into this study was 297 days from the commencement of CRT, as shown in Figure 2. This result is considered acceptable because MST obtained by second-line chemotherapy has been reported to be 8-9 months in patients with AGC refractory to first-line chemotherapy (29-31). In addition, the MST of 10 months shown in this study was comparable to the period of 12-14 months previously reported in patients with unresectable GC treated with CRT as first-line treatment (34, 35).

In conclusion, S-1 plus weekly docetaxel combined with concurrent RT was demonstrated to exhibit a tolerable toxicity profile with sufficient palliation of clinical symptoms and prolonged survival in patients with unresectable or recurrent GC refractory to first-line chemotherapy. Despite the limited number of patients treated in this study, we believe that this regimen could be a candidate for additional testing in phase II trials, paying careful consideration to the added risk of life-threatening complications associated with palliative intubation of mechanical devices in the radiation field.

Acknowledgements

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

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Received March 31, 2009
Revised June 2, 2009
Accepted June 12, 2009

癌集

スキルス胃癌への新しいアプローチ

腹膜播種陽性スキルス胃癌に対する腹腔内＋逐次全身化学療法（Hybrid Chemotherapy）

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

Scirrhous gastric cancer has a poor prognosis because of the high incidence of peritoneal metastasis. There are many cases that already have wide metastasis especially to peritoneal at a diagnosis. In addition, even if peritoneal dissemination cannot confirm, presence of a cancer cell in intra-abdominal cavity is proved to a high rate. So, even if we have done curative resection, the most common cause of death is peritoneal dissemination.

There fore, control of peritoneal dissemination is required to improve treatment outcome of the scirrhous gastric cancer that have remarkable poor prognosis.

We describe results our present studies that intraperitoneal chemotherapy followed by systemic chemotherapy (hybrid chemotherapy) plus gastrectomy on this report.

Key words: Scirrhous gastric carcinoma, Peritoneal dissemination, Intra-peritoneal chemotherapy, Systemic chemotherapy, Hybrid chemotherapy

Jpn J Cancer Clin 55(1): 59～64, 2009

はじめに

スキルス胃癌は診断時にすでに広範囲な転移を来している場合が多く，その転移は腹膜に多い．また，たとえ肉眼的に腹膜播種が確認できなくとも腹腔内に癌細胞の遊離が高率に証明されることがよく知られ，たとえ治癒切除が可能であったとしても術後には腹膜播種を生じる場合が多い[1]．この様に著しく予後が不良なスキルス胃癌の治療成績を向上させるためには腹膜播種の制御が必須である．

本稿ではわれわれの行っている腹膜播種陽性スキルス胃癌に対する腹腔内＋逐次全身化学療法（Hybrid Chemotherapy）に外科手術を加えた集学的治療方法の現在までの成績について述べる．

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*3 近畿大学医学部病理

1 ターゲットである腹膜播種巣の存在部位

癌細胞が胃漿膜を超えて浸潤した場合，もしくは脈管系を介して腹腔内に遊離した癌細胞は中皮細胞が表面を覆う腹膜上層にだけではなく，播種により肥厚したsub-methotelial layerに浸潤し病巣を形成する[2]．つまり腹膜播種を制御するためには1）腹腔内に遊離する癌細胞，2）中皮細胞近傍に存在する癌細胞，3）sub-methotelial layer深層に存在する癌細胞，これら3つの領域に存在する癌細胞を標的としなければならない．この3領域に存在する癌細胞を効率的に制御するために，われわれは抗癌剤の腹腔内投与に逐次全身化学療法を組み合わせた治療方法：Hybrid Chemotherapyを臨床研究として施行している．Hybrid Chemotherapyの理論的根拠等は他稿を参照いただきたい[3,4]．

2 治療方法の実際

近畿大学医学部外科では，各種画像診断では根治術可能と考えられるが，大型3型胃癌やスキルス胃癌など臨床的に腹膜播種を高率に疑う胃癌症例に対しては，基本的に開腹手術に先立ち，まず診断的腹腔鏡を施行している．その結果，腹膜播種が確認された症例に本治療法を施行している．レジメンは，まず腹腔内化学療法として，腹膜播種確認時にpaclitaxel 80 mg/m^{2}を生理食塩水1,000 mlに溶解し腹腔内に投与する．腹腔内に投与した薬液のドレナージは行わない．引き続き施行する全身化学療法は，可能な限り腹腔内投与後早期（少なくとも14日以内）に施行することを原則とし，レジメンは全身投与しても腹腔内への移行が良いとされているpaclitaxelとS-1を併用したOGSG（大阪消化管がん化学療法研究会）0105のレジメンに則り[5]，paclitaxel 50 mg/m^{2}をDay 1と8に投与，S-1は通常量（800 mg/m^2）をDay 1から14まで経口投与し，これを3週毎に繰り返し，少なくとも3コースは施行することとした（図1）．プロトコールでは後治療は規定していない．

われわれは本臨床研究を2003年より開始した．登録症例の中でスキルス胃癌は30例を数える．その患者背景を表1に示す．

3 化学療法の位置付けの変化

本臨床研究の症例数設定の際に，閾値MSTをJCOG0106-MF臨床試験（腹膜転移を伴う進行胃がんに対する5FU持続静注療法 vsMTX＋5-FU時間差療法による第Ⅲ相試験）の設定と同じ5カ月とし，また期待MSTをPaclitaxelの国内開発臨床第・相試験における前治療を有する未分化型胃癌を対象にした生存期間中央値を参考に9カ月と設定するpalliative[6] chemotherapyとして開始した．しかし試験開始当初に登録されたスキルス胃癌10症例のうち8症例に1年以上の生存期間を得たため．更なる治療成績の向上を目指し，化学療法の位置付けをinduction[7] chemotherapyへと変更すべく，後治療として局所療法としての手術の可能性を検討した．

4 後治療としてのDebulking Surgery

2005年よりわれわれはHybrid Chemotherapyを少なくとも3クール施行した後のEnhanced Computed Tomographyや上部消化管内視鏡検査等の画像診断で抗腫瘍効果が認められ，また播種巣に対しても治療効果が望まれる症例に対して2nd look laparoscopyを施行している．2nd look laparoscopy時に施行した腹腔洗浄細胞診ならびに腹膜生検にて，両者の陰性化が確認できた症例にはリンパ節郭清を伴う胃切除術を施行している（図2）．

リンパ節郭清の範囲は2群郭清を基本としているが，後述のように術後早期の化学療法は必須と考えているため，胃全摘の場合は脾臓温存を方針とし，脾門部のリンパ節郭清は可及的郭清としているため，D2-No. 10と表記している．

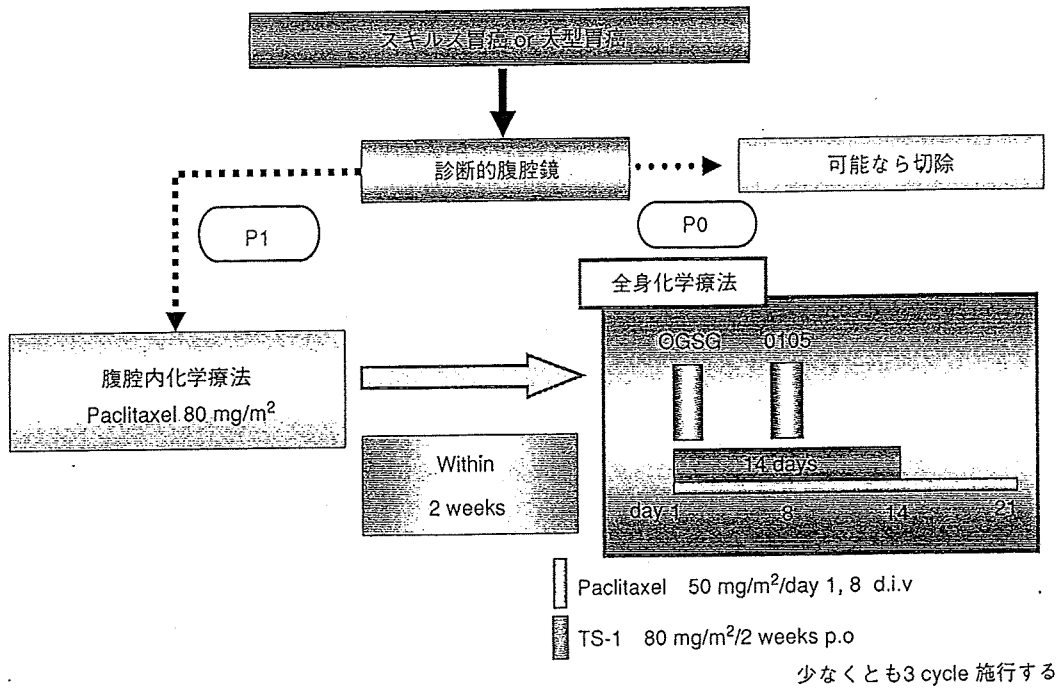


図1　近畿大学外科における腹膜播種を疑う症例に対する臨床試験

表1　スキルス胃癌30例の患者背景

年齢中央値	60.5
年齢平均	58.3
性別　男：女	17：13
PS　0：1	29：1

5 術後化学療法

この様な症例には術後は早期の化学療法の施行が必須と考え，胃全摘では14PODに，幽門側胃切除術後には7PODにWeekly Paclitaxelによる化学療法開始を基本とし，患者が胃切除後の摂食状態に慣れた時点でS-1の経口投与に移行している（図3）．

6 治療成績

2005年1月以降Hybrid Chemotherapyを施行した18例中，CT等の画像診断で抗腫瘍効果が得られたと判断した14例に2nd look laparoscopyを施行した．その中で1例のみに腹腔洗浄細胞診陽性ならびに腹膜生検で癌細胞が検出されたが，13例はCY0, pP0であり，リンパ節郭清を伴う胃切除を施行した．

腹膜播種は前述のように中皮細胞近傍のみならずsub-methotelial layer深層にも病巣を形成する．腹腔内化学療法のみでは腹腔内に投与された薬剤の腹壁への浸透距離が限られるためsub-methotelial layer深層に存在する癌細胞には効果を得られにくいと考えられるが，腹腔内化学療法と全身化学療法を組み合わせたHybrid Chemotherapy施行後の腹膜生検では，中皮細胞近傍に存在する癌細胞のみならずsub-methotelial layer深層の癌細胞をも消失し線維芽細胞の増生に置き換わっていた（図4）．

Hybrid Chemotherapyの胃壁深達度への効果を検討すると，clinicalもしくはsurgicalに13例全例がT3（SE）の診断であったが，病理学的に13例中12例がT2以下に変化しており，Hybrid Chemotherapyの効果が得られたものと考えられる．

また転移リンパ節におけるHybrid Chemotherapyの効果を検討すると，clinicalもしくはsur-

腹膜播種に対する
化学療法の効果が望める症例　2005～

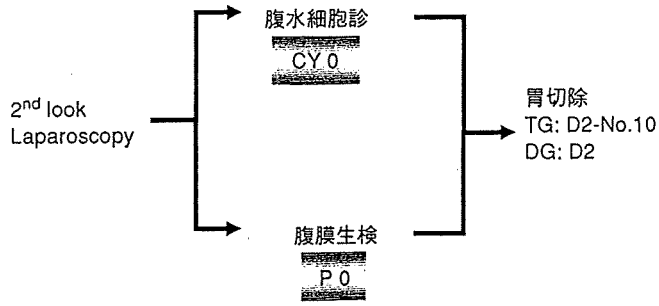


図2　後治療としての Debulking Surgery

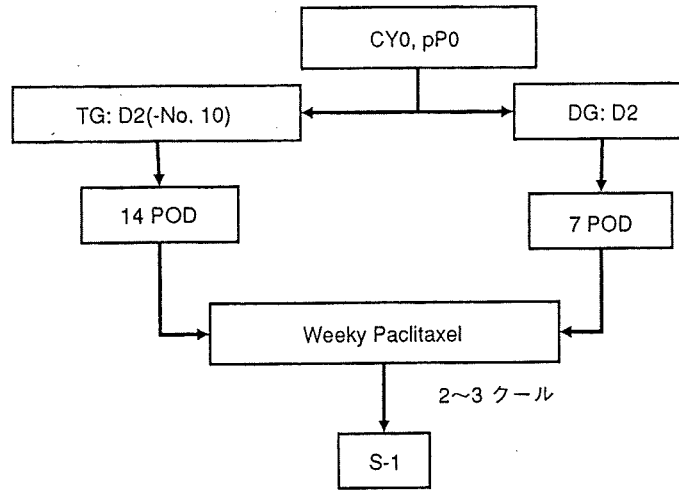
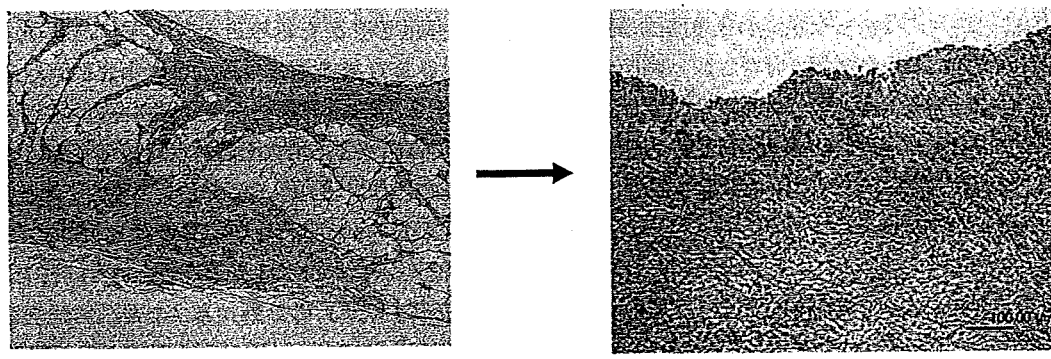


図3　術後化学療法



Hybrid Chemotherapy 前　　Hybrid Chemotherapy 後

図4　Hybrid Chemotherapy 前後の腹膜病理組織学的所見

表2　初発再発形式

• 腹壁創再発	1例
• No 13 リンパ節再発	1例
—閉塞性黄疸—胆管ステント留置	
• 腹膜播種再発	1例
• 後腹膜再発	1例
—水腎症—尿管ステント留置	重複あり

gical に N1 症例が 9 例，N2 症例が 4 例であったが，郭清したリンパ節の病理学的検索の結果，リンパ節転移の Down stage が得られた症例は N1 症例が 6 例，N2 症例においては 1 例であった．のみならず，clinical もしくは surgical に N1 と判断していた 9 症例のうち 2 症例は Hybrid Chemotherapy 後であるにも関わらず pathological N2 という結果であった．またリンパ節周囲の脂肪織内に顕微鏡的癌細胞遺残が認められる症例が，13 切除例のうち 6 例に認められた．この癌細胞の遺残が節外性リンパ節転移，もしくは播種に由来するものか判別はつき難い．しかしながら現在までに 13 切除症例中 3 例に再発を認めるが，この 3 例すべてにリンパ節周囲の脂肪織内に顕微鏡的癌細胞遺残が認められている．この 3 症例の初発再発形式を表 2 に示す．つまり，この様に癌の遺残形式を取る症例に対して現在行っている Hybrid Chemotherapy は効果不足なのかもしれない．

また Hybrid Chemotherapy 後に胃切除を施行した 13 例の現在までの生存は，MST で 877 日，1 年生存率，2 年生存率とも 61.0 パーセントである（図 5）．

まとめ

一般的には palliative chemotherapy の適応でしかない腹膜播種を伴うスキルス胃癌に対して，induction chemotherapy として Hybrid Chemotherapy＋胃切除術の成績を報告した．更なる症例の集積に加え，今後は induction chemotherapy ではなく neoadjuvant[8] chemotherapy として使用可能である薬剤ならびに投与方法の開発が望まれる．

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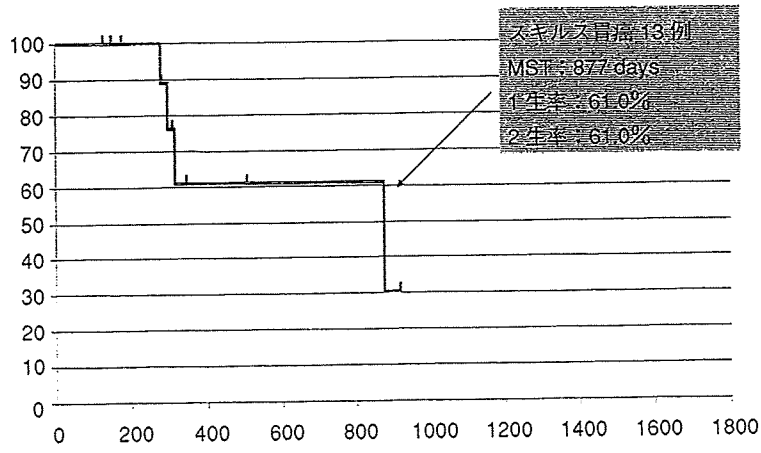

図5　胃切除後スキルス胃癌の生存曲線

討．癌と化療 33 (Supplement Ⅰ): 91–94, 2006
6) http: // www.cancer.gov / Templates / db _ alpha.aspx?CdrID=45815
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消化器科，48(5)：586-591，2009

特集II リザーバーシステムを用いた悪性腫瘍の治療

化学療法施行中に癌性腹水を生じた胃癌症例に対するリザーバーシステムを用いた腹腔内化学療法*

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Key Words : intraperitoneal chemotherapy, intraperitoneal catheter, reservoir gastric cancer

はじめに

腹膜転移に対する治療方法の一手段として腹腔内化学療法の有効性が報告されているが[1]，セカンドライン以降に用いる治療法としての腹腔内化学療法の有用性についての報告はない．われわれは全身化学療法中に癌性腹水を生じた胃癌症例に対してリザーバーシステムを用いた腹腔内化学療法を施行した．本法の手技と今までの治療成績について述べる．

有腹水症例に対するリザーバーシステム（腹腔用ポート）の設置方法

全身麻酔下での設置が望ましい．全身麻酔が不可能な場合でも腰椎麻酔を行うべきである．局所麻酔でも可能という報告も散見されるが，とくに本対象症例のように腹水を有する場合は，術中ならびに設置直後に腹圧により腹水の皮下組織への流出が生じ，播種を起こす可能性があるため避けるべきと考える．当科では全身麻酔下に診断的腹腔鏡を行い，腹水細胞診，ならびに腹膜生検を行い，腹膜播種を確認した症例にリザーバーシステムを留置している．

ポートは皮下埋め込み型の腹腔用ポートを用いる．カテーテルはシリコン製の多穴式チューブであり，細胞診用に腹水の採取も可能である．以前はダクロンのカフが装着されているタイプも販売されていたが，現在は市販されていない．

ポートは，現在のところ腹腔用ポートを患者自身が管理することはないと考えられ，また術後の患者では下腹部にはドレーン跡が存在するため，女性ならブラジャーや，ベルトの邪魔にならない季肋下部の鎖骨中線上に設置している．この部分に横切開を起き，腹直筋筋膜上にポケットを作製する．皮下脂肪が厚い患者では，術後にポートを触知することが難しい場合があることに留意しなければならない．カテーテルは筋膜上でトンネルを作成し，上腹壁動静脈が走行している腹直筋中央部は避け，やや外側から腹腔内へ挿入する．カテーテルの先端は効果判定のために行う細胞診用の腹水を採取しやすいDouglas窩近傍に留置する．カテーテルが腹膜を貫通した部分は，癌性腹水の皮下組織への流出

* Intra-peritoneal chemotherapy using intraperitoneal catheter and reservoir for the patients with malignant ascites after chemotherapy.

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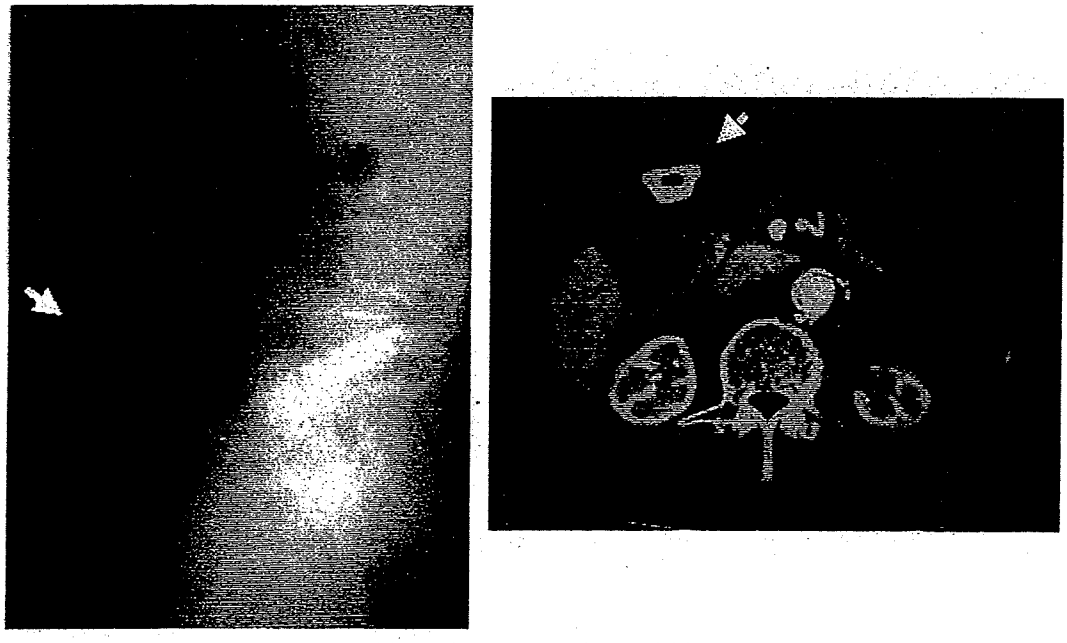

図1　ポートの反転を認めた症例
ポートの反転を認める(矢印).

を防ぐため，強固に縫合閉鎖する．その後にカテーテルとポートを接続し，ポートを筋膜にナイロン糸で固定する．以前は3点での固定を行っていたが，ポートが反転した症例を経験した後は(図1) 4点での固定を心がけている．ポートが反転した場合，用手的に整復も可能である．ポートに対する感染予防のため，第1世代セフェム系の抗生剤を予防投与する．

Paclitaxelの腹腔内投与

Paclitaxelの腹腔内投与はポート設置後1週間以上たってから行う．抗癌剤を含む薬液を腹腔内に投与することにより腹圧が上昇するが，この癌性腹水を含む薬液がカテーテル沿いにポート周囲皮下への流出する事を防ぐためである．

貯留腹水の取扱い

Paclitaxelは血漿中では蛋白と結合する．主な結合蛋白はα1-acidic glycoproteinとアルブミンであり，この結合はプラチナ系薬剤とは異なり比較的緩やかであると考えられている[2]．またpaclitaxelは，蛋白と結合した状態では細胞内へ取り込まれないため，抗腫瘍効果が発現できない可能性が生じる．腹水中でのpaclitaxelとα1-acidic glycoproteinやアルブミンとの結合，また抗腫瘍効果との関連など詳細な薬物動態については不明な点が多いが，下述のように1,000ccの生理食塩水を腹腔内に注入することにより生じる患者の腹部膨満感の軽減も顧て，可及的に癌性腹水を除去した後に投与を行っている．また除去した腹水が腹腔内に投与した薬液より多い場合は，状況に応じて経静脈的に補液を行う．

一般的には癌性腹水を有する症例は，腹腔内投与した抗がん剤の腹腔から血中へのクリアランス(peritoneal clearance)が亢進していることが多く，われわれの経験のように，症例によっては腹腔内投与とはいえGrade 3の血液毒性を診ることもある．つまり過敏症状の発現も危惧されるため，pre-medicationは経静脈投与と同様に行う．Nadir期は腹腔内投与後4,5日で現れることが多い．抗癌剤腹腔内投与特有の有害事象として腹痛があげられるが，paclitaxelを使用する限りその頻度は低い様である．

注入する薬液量は，腹腔内を十分に行き渡らす量が必要となる．明確な基準はなく，個々の症例に応じて増減する必要があると考える．当