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Ⅲ研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
辻仲利政	Randomized Controlled Trial Comparing Gastrectomy Plus Chemotherapy with Chemotherapy Alone in Advanced Gastric Cancer with A Single Non-curable Factor	Jpn J Clin Oncol	38	504-506	2008
辻仲利政	The significance of gastrectomy in advanced gastric cancer patients with non-curative factors.	Anticancer Research	28	2379-2384	2008
辻仲利政	Role of parcutaneous transhepatic biliary drainage in patients with obstructive jaundice caused by local recurrence of gastric cancer	Hepatogastroenterol	55	54-57	2008
辻仲利政	Randomized Controlled Trial of Roux-en-Y Versus Rho-Shaped-Roux-en-Y Reconstruction After Distal Gastrectomy for Gastric Cancer.	World Journal of Sugery	33	290-295	2008
辻仲利政	Japan Clinical Oncology Group. D2lymphadenectomy alone or with para-aortic nodal dissection for gastrin cancer.	Int J Clin Oncol	13	479-482	2008
辻仲利政	Current status of chemoradiotherapy for gastric cancer in Japan.	Int J Clin Oncol	13	117-120	2008

辻仲利政	Phase II study of a combination of S-1 and paclitaxel in patients with unresectable or metastatic gastric cancer.	Oncology.	74(1-2)	37-41	2008
山上裕機	Multiple early gastric cancer with gastritis cystica profunda showing various histological type	Hepatogastroenterol	.55	1150-2	2008
山上裕機	Analysis of the prognostic factors and evaluation of surgical treatment for synchronous liver metastases from gastric cancer.	Langenbecks Arch Surg.	Epub ahead of print	425-429	2008
山上裕機	Laparoscopic resection for gastrointestinal stromal tumors of the stomach.	Am J Surg	196	425-429	2008
栗田　啓	幽門側胃切除術後過食を契機とした胃破裂の1例	日消外会誌	42	253-256	2009
寺島雅典	胃癌手術とリンパ節郭清	コンセンサス癌治療	7(4)	186-189	2008
寺島雅典	フッ化ピリミジンと遺伝子多型	癌と化学療法	35(7)	1101-1104	2008
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今本治彦	抗癌剤単回腹腔内投与+逐次複数回全身投与療法の腹膜播種を伴う胃癌症例に対する効果	癌の臨床	54(5)	329-336	2008

今本治彦	胃癌 –基礎・臨床研究のアップデート・ Ⅷ 再発・転移 腹膜播種 化学療法 –抗癌剤腹腔内投与・全身化学療法併用療法。	日本臨床	66	596-602	2008

Reprinted from

Jpn J Clin Oncol 2008;38(7)504–506
doi:10.1093/jjco/hyn058

Randomized Controlled Trial Comparing Gastrectomy Plus Chemotherapy with Chemotherapy Alone in Advanced Gastric Cancer with A Single Non-curable Factor: Japan Clinical Oncology Group Study JCOG 0705 and Korea Gastric Cancer Association Study KGCA01

Kazumasa Fujitani[1], Han-Kwang Yang[2], Yukinori Kurokawa[1], Do Joong Park[3], Toshimasa Tsujinaka[1], Byung-Joo Park[4], Haruhiko Fukuda[5], Sung Hoon Noh[6], Narikazu Boku[7], Yung-Jue Bang[8], Mitsuru Sasako[9] and Jong-Inn Lee[10] for the Gastric Cancer Surgical Study Group of Japan Clinical Oncology Group and Korea Gastric Cancer Association

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Received March 15, 2008; accepted June 10, 2008; published online July 9, 2008

A randomized controlled trial has started in both Japan and Korea to evaluate the role of gastrectomy in the management of incurable advanced gastric cancer (AGC). Patients with AGC diagnosed as having a single non-curable factor are randomized to gastrectomy plus chemotherapy or chemotherapy alone. Surgeons at 33 specialized centers in Japan and at 15 high-volume hospitals in Korea will recruit 330 patients. Primary end-point is overall survival, and secondary end-points are progression-free survival and adverse events associated with either gastrectomy or chemotherapy.

Key words: gastrectomy – chemotherapy – advanced gastric cancer – non-curable factor – randomized controlled trial

INTRODUCTION

The prognosis of advanced gastric cancer (AGC) patients with non-curable factors, such as hepatic and peritoneal metastases, is poor and most of them die within 1 year. For these patients, the role of gastrectomy remains controversial. However, gastrectomy is the preferred procedure for these patients, even in the absence of any symptoms such as bleeding and stenosis, based on the results of retrospective studies showing that the procedure confers a survival benefit. In the literature (1–9), overall survival of 8.0–12.2 months is reported with gastrectomy compared with 2.4–6.7 months without gastrectomy, and the survival benefit of gastrectomy is obtained only in patients with a single non-curable factor. Obviously, there should be enormous selection bias in these data, generally speaking in favor of surgical patients. Furthermore, chemotherapy alone has recently shown, for the first time, a median survival time over 1 year in AGC deemed incurable (10). These situations warrant a prospective randomized controlled trial designed to investigate the role of gastrectomy in AGC with a single non-curable factor. The Clinical Trial Review Committee of the Japan Clinical Oncology Group (JCOG) approved the following protocol on 18 December 2007, and the study was activated on 4 February 2008.

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PROTOCOL DIGEST OF THE JCOG0705/ KGCA01

Purpose

The purpose of this trial was to investigate the superiority of gastrectomy followed by chemotherapy to chemotherapy alone in clinically stage IV AGC with a single non-curable factor, in terms of survival benefit and safety associated with gastrectomy or chemotherapy.

Study Setting

The study was a multi-institutional (33 specialized centers in Japan and 15 high-volume hospitals in Korea) randomized controlled trial.

Resources

Grants-in-Aid for Cancer Research (17S-3, 17S-5), from the Ministry of Health, Labor and Welfare, Japan. Grants for Cancer Research, from the Korean Gastric Cancer Association, Korea.

End-Points

The primary end-point is overall survival. The secondary end-points are progression-free survival and adverse events associated with gastrectomy or chemotherapy.

Eligibility Criteria

Tumors are staged according to the Japanese Classification of Gastric Carcinoma (11).

Inclusion Criteria

Patients are included in the trial if they meet all of the following criteria: (i) histologically proven primary gastric adenocarcinoma, (ii) presence of only one of the following patterns of metastasis, which is confirmed by both computed tomography (CT) scan and staging laparoscopy (or open laparotomy): (a) hepatic metastasis (H1) (2–4 lesions, maximum diameter <5 cm), (b) peritoneal dissemination (P1) without massive ascites or intestinal obstruction or (c) extensive para-aortic lymph node metastasis (No. 16a1 and/or b2), (iii) clinical T1-3, (iv) no evidence of para-aortic and/or retropancreatic lymph node metastasis (i.e. N0–2) in the cases of hepatic or peritoneal metastasis, (v) no evidence of other distant metastasis than H1, P1 or LN 16a1/b2, (vi) no apparent pleural effusion, (vii) length of esophageal invasion 3 cm or less with no need of thoracotomy for resection, (viii) not stump carcinoma, (ix) aged 20–75 year old, (x) performance status (PS) of 0 or 1 on Eastern Cooperative Oncology Group (ECOG) scale, (xi) sufficient oral intake without active bleeding from the gastric tumor, (xii) no prior treatment of chemotherapy or radiation therapy against any other malignancies, and no prior treatment for gastric cancer except EMR (endoscopic mucosal resection), (xiii) adequate organ functions defined as indicated below: (a) WBC $\geq 3000/mm^3$, WBC $\leq 12\ 000/mm^3$, (b) Hb ≥ 8.0 g/dl without any transfusion 2 weeks before enrollment, (c) Plt $\geq 100\ 000/mm^3$, (d) AST ≤ 100 IU/l, (e) ALT ≤ 100 IU/l, (f) T.Bil ≤ 2.0 mg/dl, (g) Cr ≤ 1.2 mg/dl, (h) Ccr ≥ 60 ml/min/body and (xiv) written informed consent.

Exclusion Criteria

Patients are excluded if they meet any of the following criteria: (i) active double cancer (synchronous double cancer and metachronous double cancer within five disease-free years), excluding carcinoma *in situ* (lesions equal to intraepithelial or intramucosal cancer), (ii) pregnant or breast-feeding women, (iii) severe mental disorder, (iv) systemic administration of corticosteroids, (v) medication of furucytocin, fenytoin or warfarin, (vi) active bacterial infection or mycosis, affecting systemic condition, (vii) unstable angina or myocardial infarction within 6 months of the trial, (viii) unstable hypertension, (ix) diabetes mellitus, uncontrolled or controlled with insulin, (x) severe respiratory disease requiring continuous oxygen therapy.

Randomization

After confirmation of the above criteria, registration is made by telephone call or fax to the JCOG Data Center in Japan, and by web system to Seoul National University Hospital (SNUH) Data Center in Korea. Patients are randomized in each country by a minimization method of balancing the arms according to institution, nodal status (N0–1/N2–3) and non-curable factor (hepatic/peritoneal/para-aortic metastasis).

Treatment Methods

Gastrectomy Plus Chemotherapy

Either a total, distal or proximal gastrectomy with D1 lymph node dissection is performed depending on the tumor location with the metastatic lesions untouched. Neither complete D2 lymphadenectomy nor combined resection of adjacent organs except for gallbladder, mesocolon and diaphragm is acceptable. Within 8 weeks after surgery, the patient is placed on a chemotherapy regimen, S-1 + CDDP. Oral S-1 is administered at a dose of 80 mg/m^2/day for 3 consecutive weeks followed by a 2-week rest. Cisplatin is delivered on Day 8 at a dose of 60 mg/m^2. This regimen is repeated every 5 weeks until disease progression.

Chemotherapy Alone

Patients receive the same chemotherapy as described above without any operation until disease progression.

Follow-up

Patients are assessed every months to detect any adverse events with verbal interview, physical examination and blood tests, including a complete blood cell count and measurements of liver and renal function, until progressive disease. Abdominal CT scan and measurements of CEA and CA19-9 are carried out every 3 months.

Study Design and Statistical Methods

This trial is designed to evaluate the superiority of gastrectomy followed by chemotherapy to chemotherapy alone in terms of overall survival. The hypothesis to be tested is that 2-year overall survival on gastrectomy followed by chemotherapy is greater than that (20–25%) obtained by chemotherapy alone by 10%. If a 10% improvement in a 2-year overall survival rate is demonstrated, gastrectomy followed by chemotherapy will be the preferred treatment. The planned sample size is 330, 165 cases per arm, with 2 years follow-up after 4 years of accrual. This will provide an 80% power with a one-sided alpha of 5%.

Interim Analysis, Monitoring and Audit

Two interim analyses are planned, with adjustments for repeated comparisons taken into account by the Lan and DeMets method. We use the O'Brien–Fleming-type alpha spending function. The Data and Safety Monitoring Committee (DSMC) of the JCOG independently reviews the interim analysis report and will consider stopping the trial early, in agreement with SNUH Data Center. Central monitoring is performed by the respective Data Center in each country to ensure data submission, patient eligibility, protocol compliance, safety and on-schedule study progress. The monitoring reports are submitted to and reviewed by the respective Data Center independently every 6 months. The monitoring summary is exchanged between the two countries semiannually. Audits of the participating facilities are also carried out independently in each country, and brief summaries are exchanged.

PARTICIPATING INSTITUTIONS

Japan: Iwate Medical University, Sendai National Hospital, Miyagi Cancer Center, Yamagata Prefectural Central Hospital, National Defense Medical College, Saitama Cancer Center, National Cancer Center Hospital East, National Cancer Center Hospital, Tokyo Metropolitan Komagome Hospital, Tokyo Medical and Dental University, Cancer Institute Hospital, Tokyo Metropolitan Bokutoh Hospital, Kanagawa Cancer Center, Niigata Cancer Center Hospital, Nagaoka Chuo General Hospital, Tsubame Rosai Hospital, Toyama Prefectural Central Hospital, Gifu Municipal Hospital, Shizuoka Prefectural General Hospital, Aichi Cancer Center, Fujita Health University, Kyoto 2nd Red Cross Hospital, Kinki University, Osaka Medical Center for Cancer and Cardiovascular Diseases, National Osaka Medical Center, Osaka Medical College, Toyonaka Municipal Hospital, Sakai Municipal Hospital, Itami City Hospital, Wakayama Medical University, Hiroshima City Hospital, National Shikoku Cancer Center, Oita University.

Korea: Ajou University Hospital, Chonnam University Hwasun Hospital, Dong-A University Hospital, Hanyang University Hospital, Kangnam St Mary's Hospital, Korea Cancer Center Hospital, Korea University Guro Hospital, Kosin University Hospital, Kyungpook University Hospital, National Cancer Center, Samsung Medical Center, Seoul National University Hospital, Seoul National University Bundang Hospital, Yonsei University Severance Hospital, Yonsei University Youngdong Hospital.

Conflict of interest statement

Mitsuru Sasako states that he has received honoraria from Taiho Pharmaceutical Company for giving educational lectures in 2007.

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ANTICANCER RESEARCH 28: 2379-2384 (2008)

The Significance of Gastrectomy in Advanced Gastric Cancer Patients with Non-curative Factors

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Abstract. *Background: The role of gastrectomy in the treatment of advanced gastric cancer patients with non-curative factors remains controversial. We investigated prognostic factors and evaluated the role of gastrectomy in such patients. Patients and Methods: Eighty-eight advanced gastric cancer patients with non-curative factors were prospectively studied. The patients were categorized into the following two groups: Group A: 52 patients who underwent gastrectomy and subsequently received chemotherapy, Group B: 36 patients who received chemotherapy alone. Results: The median survival times of group A and B patients were 351 and 182 days, respectively (p=0.008). Multivariate analysis showed that gastrectomy was the only positive independent prognostic factor, with no effect on the results of chemotherapy. There was no significant difference in the duration of hospital stay between patients of the two groups, while significantly longer maintenance of oral intake was observed for group A. Conclusion: In advanced gastric cancer patients with non-curative factors, gastrectomy was beneficial for survival with longer maintenance of oral intake.*

The prognosis of advanced gastric cancer (AGC) patients with non-curative factors, such as hepatic and peritoneal metastases, is poor and most of them die within one year. For these patients, opinion is divided on the role of gastrectomy while leaving metastatic lesions. However, gastrectomy is the preferred procedure for AGC, even in the absence of any symptoms such as bleeding and stenosis, based on the results of retrospective studies showing that the procedure confers a survival benefit (1, 2).

On the other hand, despite the potential survival benefit of gastrectomy, patient quality of life (QOL), such as duration of hospital stay and oral intake, may be negatively influenced by gastrectomy because of postoperative morbidities. In addition, gastrectomy may reduce the efficacy and safety of chemotherapy, which is considered to be an integral part of the treatment for AGC patients, due to delayed commencement of postoperative chemotherapy or reduced compliance with chemotherapy.

The present study was conducted to investigate whether gastrectomy followed by chemotherapy was more beneficial than chemotherapy alone in AGC patients with non-curative factors.

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Key Words: Gastrectomy, non-curative factor, prognostic factor, advanced gastric cancer.

Patients and Methods

Patient characteristics. This study was conducted on 88 patients diagnosed with AGC having non-curative factors at Osaka National Hospital between Jan 1, 1999 and Dec 31, 2004. These patients were categorized into the two groups shown in Table I. A total of 52 patients in group A, 38 males and 14 females with a median age of 69 (range: 43-87) years, underwent gastrectomy with subsequent chemotherapy. Thirty-six patients in group B, 27 males and 9 females with a median age of 66 (range: 19-80) years, received chemotherapy alone without gastrectomy. All of the patients had a performance status (PS) of 2 or less on the Eastern Cooperative Oncology Group (ECOG) scale at initial diagnosis and none had received prior chemotherapy or radiation therapy. Most patients had advanced cancer of T3 or deeper, with positive lymph node metastases. Histologically, around one-third of patients had intestinal-type adenocarcinoma and two-thirds had diffuse-type adenocarcinoma. The patients had a range of non-curative factors. If a tumor showed infiltration to adjacent organs (T4) and was deemed radically unresectable, such a T4 tumor was regarded as a non-curative factor. Para-aortic lymph node metastasis (N3) was also considered to be a non-curative factor. In addition, hepatic metastasis (H), peritoneal metastasis (P), positive cytology of abdominal lavage (CY) and distant metastasis (M) were all regarded as non-curative factors. The classifications of T-stage, N-stage and non-curative factors were made in accordance with the guidelines of the Japanese Gastric Cancer Association (3). As for the number of non-curative factors, 38 patients in group A had a single non-curative factor while 14 patients had two or more; 15 patients in group B had a single factor and 21 patients had two or more.

Various chemotherapeutic agents were administered to the patients in both groups. More than half the patients received an oral fluoropyrimidine derivative, such as S-1 (4), UFT (a combination

Table I. *Patient characteristics.*

	Group A	Group B	*p*-value
Number of patients	52	36	
Male/female	38/14	27/9	NS
Median age, years (range)	69 (43-87)	66 (19-80)	NS
PS 0/1/2	28/19/5	14/17/5	NS
T stage: 2/3/4	4/28/20	1/23/12	NS
N stage: 0/1/2/3	2/17/23/10	3/13/5/15	**0.010**
Histological type: intestinal/diffuse	19/33	11/25	NS
Noncurative factor: T4/N3/H/PCY/M	2/10/15/37/4	12/15/16/18/8	**0.005**
Number of noncurative factors: 1/2≤	38/14	15/21	**0.004**
Chemotherapeutic agents:			NS
S-1/UFT/5'-DFUR	39	27	
Cisplatin	12	15	
Irinotecan	16	14	
Paclitaxel	20	11	

Group A consisted of 52 patients undergoing gastrectomy and subsequent chemotherapy; Group B comprised 36 patients receiving chemotherapy alone without chemotherapy. PS: performance status, T4: tumor infiltrating to adjacent organs, N3: para-aortic lymph node metastasis, H: hepatic metastasis, P: peritoneal metastasis, CY: positive cytology of abdominal lavage, M: distant metastasis. UFT: uracil-tegafur, 5'DFUR: 5'-deoxy-5-fluorouridine, NS: not significant. *P*-values were calculated by χ^2 test.

of uracil and tegafur at a molar ratio of 4 to 1) and 5'-DFUR (5'-deoxy-5-fluorouridine). Intravenous agents such as cisplatin, irinotecan and paclitaxel were also administered to fewer than half the patients, as shown in Table I.

Analyses of prognostic factors. The therapeutic course of each patient was followed until death or until Dec 31st 2006. Seven patients in group A were alive on Dec 31st 2006 and treated as censored observations for survival analysis. The survival time was defined as the duration from the date of starting therapy, gastrectomy or chemotherapy, to death or Dec 31st 2006.

A univariate analysis was used to assess the association between each clinicopathological factor and overall survival. A multivariate analysis was performed to identify variables independently associated with survival.

QOL assessment. Duration of hospital stay and oral intake in each patient were estimated and used to assess the patient's QOL. The following indices were set: hospitalization index, the duration of hospital stay as a proportion of the overall survival period; and ingestion index, the duration of the period in which oral intake was maintained as a proportion of the overall survival period. These were used to make comparisons between the two groups.

Efficacy and safety of chemotherapy. Response to chemotherapy in each patient was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) (5) whenever possible. Toxicities of chemotherapy in all patients were scored according to the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE) (6).

Statistical analysis. Stat View software Version 5.0 (SAS Institute Inc. Cary, NC, USA.) was used for all statistical analyses and a *p*-value of less than 0.05 was considered significant. The χ^2 test was employed to evaluate differences in proportions, and the differential significances of age, hospitalization index and ingestion index were determined by the Mann-Whitney test. The survival rates were calculated according to the Kaplan-Meier method and difference was evaluated by the log rank test. Cox's proportional hazards regression model was used to identify prognostic factors for survival.

Results

Overall survival and prognostic factors. Overall survival time was compared between the two groups. The median survival time (MST) of group A was 351 days, while that of group B was 182 days, with a significant difference between the two groups (p=0.008), as shown in Figure 1. Actual survival rates of 48.1% at 1 year and 20.2% at 2 years were obtained in group A, while Group B had rates of 16.7% at 1 year and 0% at 2 years. The results of univariate analysis of various clinicopathological factors for overall survival are summarized in Table II. Absence of gastrectomy (hazard ratio: 2.165, p=0.001), existence of T4 factor (hazard ratio: 2.190, p=0.0108), existence of N3 factor (hazard ratio: 1.897, p=0.0096), and presence of multiple non-curative factors (hazard ratio: 2.056, p=0.0020) were identified as significantly negative prognostic factors for overall survival. Multivariate analysis showed that only absence of gastrectomy was an independent negative prognostic factor (relative risk 1.745, p=0.0282), as shown in Table III.

Hospitalization Index and Ingestion Index. As shown in Table IV, the Hospitalization Index was not different between the two groups. On the other hand, the Ingestion Index was significantly higher in group A than in group B.

Influence of gastrectomy on efficacy and safety of chemotherapy. As shown in Table V, 43 patients (82.7%) in group A received chemotherapy after gastrectomy with the exception of 9 patients who had postoperative morbidities. The average interval between gastrectomy and commencement of chemotherapy was 44 days in group A. Twenty-five patients in group A had only P/CY factors, which were not evaluable on RECIST. In group B, all the patients received chemotherapy and had evaluable lesions, though 13 patients underwent the following surgical interventions prior to chemotherapy: exploratory laparotomy in 6, gastroenteroanastomosis in 4, jejunostomy in 1, and insertion of metallic stent into pyloric stenosis in 2. The best response to chemotherapy demonstrated in the entire therapeutic period in each patient is shown in Table V; response rates of around 25% were obtained in both groups with no significant difference (p=0.7515). Hematological and nonhematological

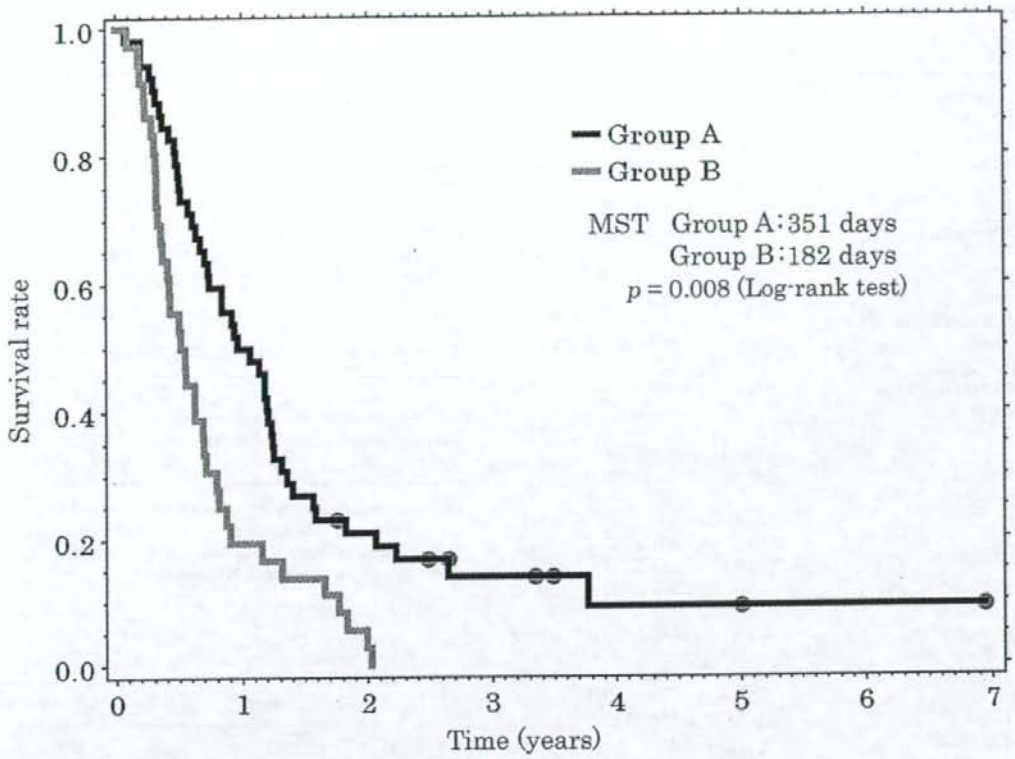

Figure 1. *Survival curves of the patients in Group A and B.*

adverse events during the entire chemotherapeutic period in both groups are shown in Table VI. There was no significant difference between the two groups, with no chemotherapy-related deaths in either group.

Discussion

An average of 15-30% of patients with newly diagnosed advanced gastric cancer (AGC) have non-curative factors that are detected initially at surgical staging by laparoscopy or laparotomy (7-11). When the disease is deemed incurable, treatment of AGC remains investigational in terms of prognosis and QOL.

Regarding the prognosis of patients with incurable AGC, some reports have shown the survival benefit of gastrectomy (1, 2, 10, 12-16). An MST of 8.0-12.2 months was reported with gastrectomy, compared to 2.4-6.7 months without gastrectomy. In addition, the survival benefit of gastrectomy was obtained only in patients with a single non-curative factor (1, 10, 12, 13, 16). In accordance with these findings, our patients showed an MST of 351 days with gastrectomy and 182 days without gastrectomy, a significant difference (p=0.008). In addition, the presence of a single non-curative factor was identified as a prognostic factor by univariate analysis as shown in Table II, and multivariate analysis showed that only the presence of gastrectomy was independently correlated with better prognosis (relative risk 0.573, p=0.0282) in Table III.

With regard to the safety of gastrectomy in AGC patients with non-curative factors, morbidity rates of 30-40% (11-13, 17, 18) and mortality rates of around 10% (11-14, 17-19) have been reported. Our patients had an operative morbidity of 21.2% and mortality of 3.8% (data not shown). These are good figures and might have partly contributed to the better survival of our patients with gastrectomy.

Satisfactory palliation of symptoms and QOL are two other principal objectives in the care of patients with non-curative gastric cancer. There have been few reports on the objective assessment of QOL in these patients. However, Ouchi *et al.* assessed hospital-free survival as a indicator of QOL and reported that total gastrectomy performed in patients with local

Table II. *Univariate analysis of various prognostic factors.*

	Hazard ratio	95% CI	*p*-value
Gastrectomy			
Absent	2.165	1.368-3.425	**0.0010**
Gender			
Female	0.826	0.500-1.366	0.4569
Age			
≥70	1.241	0.792-1.946	0.3461
Perfomance Status			
0	1.000		0.5727
1	0.389	0.119-1.278	
2	0.287	0.082-1.000	
Macroscopic type of tumor			
3&4	1.068	0.637-1.795	0.8016
Histology			
Diffuse type	0.890	0.559-1.417	0.6242
T stage			
2	1.000		0.5216
3	1.634	0.582-4.588	
4	1.838	0.637-5.305	
N stage			
0	1.000		0.2457
1	1.730	0.601-4.983	
2	1.958	0.664-5.774	
3	2.646	0.902-7.760	
T4 factor			
Present	2.190	1.199-4.000	**0.0108**
N3 factor			
Present	1.897	1.168-3.081	**0.0096**
H factor			
Present	1.160	0.734-1.832	0.5255
P/CY factor			
Present	0.825	0.726-1.293	0.4008
M factor			
Present	1.468	0.791-2.724	0.2300
No. of non-curative factors			
≥2	2.056	1.302-3.244	**0.0020**

P-values were calculated by the Cox's proportional hazards regression model.

Table III. *Multivariate analysis of prognostics factors.*

	Hazard ratio	95% CI	*p*-value
Gastrectomy			
Absent	1.745	1.061-2.871	0.0282
No. of non-curative factors			
≥2	1.464	0.752-2.851	0.2623
T4 factor			
Present	1.342	0.650-2.768	0.4265
N3 factor			
Present	1.228	0.638-2.364	0.5386

Table IV. *Hospitalization index and ingestion index.*

	Group A	Group B	*p*-value
Hospitalization index	0.311	0.406	0.066
Ingestion index	0.871	0.798	0.003

Hospitalization Index: the duration of hospital stay relative to the overall survival period. Ingestion Index: the duration of the period in which oral intake was maintained relative to the overall survival period. *P*-values were calculated by the Mann-Whitney test.

Table V. *Best response to chemotherapy.*

	Group A	Group B
CR	3	1
PR	1	9
SD	6	14
PD	8	12
NE	25	0
RR	22.2%	27.8%

RR: response rate, CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, NE: not evaluable.

or no peritoneal metastasis and distal gastrectomy showed a better outcome for hospital-free survival than total gastrectomy performed with extensive peritoneal metastasis (2). Hoya *et al.* adopted hospitalization, the average volume of oral intake and variation in body weight for assessing QOL (20). They reported that in patients who underwent total gastrectomy, hospitalization was longer, the average volume of oral intake was less and the variation in body weight was greater than in patients with unresectable tumors. We evaluated the length of hospital stay after initiation of treatment and the period for which oral intake was maintained as objective indicators of QOL. In Table IV, it can be seen that gastrectomy was useful for maintaining a longer period of oral intake, while there was no significant difference between total gastrectomy and distal gastrectomy (data not shown).

Although chemotherapy is an integral part of the treatment of AGC, it may be affected by surgery due to delayed commencement of postoperative chemotherapy or reduced compliance with chemotherapy after surgery. However, in our patients, gastrectomy had no effect on either efficacy or safety of chemotherapy, as shown in Tables V and VI. There are few reports that address the question of whether gastrectomy performed in patients with non-curative factors is beneficial in terms of efficacy, safety and compliance with chemotherapy in a course of adjuvant chemotherapy.

In conclusion, gastrectomy was shown to be beneficial for survival with oral intake maintained for a longer period and it did not affect the results of chemotherapy in AGC patients with non-curative factors. These results warrant a prospective

Original Paper

Role of Percutaneous Transhepatic Biliary Drainage in Patients with Obstructive Jaundice Caused by Local Recurrence of Gastric Cancer

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KEY WORDS: Obstructive jaundice; Percutaneous transhepatic biliary drainage (PTBD); Gastric cancer; Local recurrence; Chemotherapy

ABBREVIATIONS: Percutaneous Transhepatic Biliary Drainage (PTBD); Total bilirubin (T-bil); Median Survival Time (MST); Randomized Controlled Trial (RCT); Colony-Stimulating Factor (G-CSF); Quality Of Life (QOL)

ABSTRACT

Background/Aims: We reviewed the medical records of patients with obstructive jaundice caused by the local recurrence of gastric cancer to clarify the role of percutaneous transhepatic biliary drainage (PTBD).

Methodology: Eleven patients with a mean age of 60.1 years (range: 51-71 years) underwent PTBD because of obstructive jaundice caused by the extrahepatic recurrence of gastric cancer.

Results: Jaundice was relieved in all the patients, and the serum total bilirubin (T-bil) level decreased from 12.2 to 2.1mg/dL. No major complications associated with the execution of PTBD occurred. Although various symptoms caused by jaundice, such as anorexia, itching, nausea, abdominal pain, and fever, were relieved in all the patients within one week after PTBD, general fatigue persisted in 3 patients and abdominal fullness persisted in one. Seven of the 11 patients were discharged from the hospital after the execution of PTBD and remained at home for a median of 93 days. The median survival time (MST) of the remaining 4 patients who could not be discharged was 48 days. Chemotherapy was added in 5 patients after the execution of PTBD; these patients exhibited a significantly longer MST of 247 days, compared to 62 days among the patients who did not receive chemotherapy (P=0.0176).

Conclusions: PTBD was safely conducted and improved the quality-of-life of patients with obstructive jaundice caused by the local recurrence of gastric cancer. Furthermore, the use of chemotherapy after PTBD might prolong patient survival although RCT (randomized controlled trial) study should be performed to assess the precise effect of chemotherapy after PTBD.

INTRODUCTION

Extrahepatic biliary obstructions resulting in obstructive jaundice can be caused by various kinds of metastatic carcinoma originating from the colon, breast, lung, cervix, melanoma, and stomach (1,2). The incidence of extrahepatic biliary obstruction associated with the local recurrence of gastric cancer has been reported to be 1.4 to 2.3% (3,4). Since impaired hepatic function, characterized by a high serum total bilirubin (T-bil) level, contraindicates active chemotherapy in patients with malignant biliary obstructions, the prognosis of patients is generally poor (5). However, effective biliary drainage may improve the hepatic function of the patient, making it subsequently feasible to add chemotherapy to their treatment regimen and possibly leading to an improved prognosis. Therefore, we reviewed the medical records of patients with obstructive jaundice caused by the local recurrence of gastric cancer to clarify the role of percutaneous transhepatic biliary drainage (PTBD).

Hepato-Gastroenterology 2008; 55:54-57

METHODOLOGY

Patient Characteristics

Between October 1998 and March 2004, 873 patients underwent a gastrectomy for the treatment of primary gastric cancer at the Department of Surgery, Osaka National Hospital (Osaka, Japan). Among them, 11 patients (8 men and 3 women; mean age, 60.1 years; age range, 51-71 years) developed extrahepatic biliary obstructions caused by lymph node recurrences along the hepatoduodenal ligament. The clinical characteristics of the patients are shown in Table 1. Five patients had previously undergone a distal gastrectomy and six patients had undergone a total gastrectomy.

RESULTS

Ten of the 11 patients had primary gastric cancers located in the lower third of their stomachs. Morphologically, 4 patients had scirrhous-type advanced gastric cancer and 7 patients had ulcerative-type gastric cancer. Histologically, diffuse-type adenocarcino-

ma was observed in 7 patients. The primary tumor had invaded transmurally beyond the serosa in 9 of the 11 patients. Seven patients had stage IV disease according to the TNM classification (6); the N3 nodes were involved in 6 patients, and three patients had peritoneal dissemination. A curative R0 resection was performed in 7 patients. At the onset of jaundice, 5 patients had a performance status (PS) of 1 and 5 patients had a PS of 2, according to the Eastern Cooperative Oncology Group (ECOG) scale. The median interval between the initial gastrectomy and the onset of obstructive jaundice was 359 days (range: 83-874 days). Other than the metastatic lymph nodes along the hepatoduodenal ligament, 8 patients had distant metastatic lesions involving the liver in 6 patients, the peritoneum in 5 patients (without massive ascites), and the bone in one patient.

Safety and Efficacy of PTBD

All the patients underwent PTBD, and their jaundice was effectively relieved: the serum T-bil level decreased from 12.2mg/dL (range: 4.6-21.3mg/dL) to 2.1mg/dL (range: 0.9-4.7mg/dL) mg/dL. No major complications associated with the execution of PTBD occurred. During the follow-up period after the initial PTBD, 8 of the 11 patients developed incidental cholangitis; these patients were conservatively treated with antibiotics, and their conditions improved. Tube obstructions occurred in 3 patients within a week after the insertion of the PTBD tube, requiring that the tube be exchanged. The obstructions were caused by bile sludge in 1 patient and tube dislocations in 2 patients. Transient hemobilia was seen in one patient.

Various symptoms caused by jaundice, such as anorexia, itching, nausea, abdominal pain, and fever, were relieved in all the patients within one week after PTBD. However general fatigue persisted in 3 patients and abdominal fullness persisted in one patient (Table 2). Seven out of the 11 patients were discharged from the hospital after the execution of PTBD and remained at home for a median of 93 days (range: 3-285 days).

Chemotherapy after PTBD

After their jaundice had been relieved using PTBD, 5 patients received chemotherapy, consisting of UFT (tegafur/uracil), irinotecan + cisplatin, S1 (tegafur/CDHP/Potassium Oxonate), S1 + paclitaxel, and 5-fluorouracil + methotrexate, respectively, because these patients fulfilled the following criteria: 1) age ≤76 years; 2) ECOG performance status ≤2; 3) normal bone marrow function (white blood cell count ≥4000/mm³, platelet count ≥100,000/mm³, hemoglobin ≥10g/dL); 4) normal renal function (creatinine concentration <1.5mg/dL); 5) absence of myocardial, hepatic (T-Bil <2.0mg/dL), and neurologic impairment; and 6) verbal and written informed consent before initiation of chemotherapy. When the clinical characteristics of the patients that did and did not receive chemotherapy were compared, the mean

TABLE 1 Clinical Characteristics of 11 Patients with Obstructive Jaundice caused by the Local Recurrence of Gastric Cancer

Case	Age	Sex	Gastrectomy	Location	Morphology	Histology (intestinal /diffuse)	Stage	Curability	Interval (Gastrectomy~ Onset of jaundice)(days)	Maximum value of serum T-Bil (mg/dL)	PS	Combined distant metastasis
1	59	f	distal	L	ulcerative	diffuse	IIIA (t3n1)	B	258	15.7	1	H
2	52	f	distal	L	ulcerative	intestinal	IIIA (t2bn2)	B	145	10.0	1	H
3	67	m	total	LMU	scirrhous	diffuse	IV (t3n3)	B	717	8.6	1	
4	51	f	total	U	scirrhous	diffuse	IV (t3n3)	B	874	21.3	2	P
5	67	m	distal	LM	ulcerative	diffuse	IIIA (t3n1)	A	624	19.0	2	bone H,P
6	56	m	total	LM	ulcerative	diffuse	IV (t4n2H1P1)	C	348	10.4	1	H,P
7	71	m	distal	L	ulcerative	intestinal	IV (t3n3P1CY1)	#6	221	9.9	0	H,P
8	60	m	total	LMU	ulcerative	diffuse	IV (t3n3P1)	C	184	4.6	1	P
9	55	m	total	LM	scirrhous	intestinal	IV (t3n3)	A	83	9.0	2	
10	69	m	total	LMU	scirrhous	diffuse	II (t2bn1)	A	275	13.4	2	
11	54	m	distal	L	ulcerative	intestinal	IV (t4n3)	C	217	12.3	2	H

m: male, f: female, *L/M/U*: lower / middle / upper third of the stomach, H: liver metastasis, P: peritoneal dissemination, CY: cytology of peritoneal lavage.

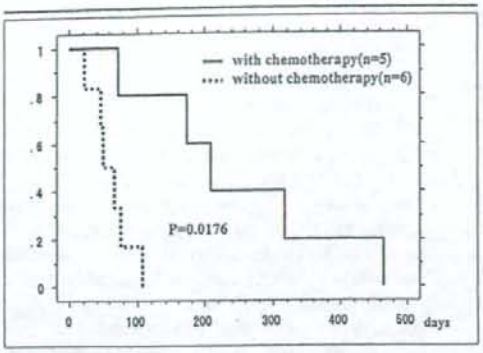

FIGURE 1 Survival after PTBD.

PTBD-induced improvement in the serum T-bil level was significantly lower in the patients who received chemotherapy, as shown in Table 3 (P=0.03). During the chemotherapy regimens, grade 4 neutropenia was observed in two patients, requiring the administration of granulocyte colony-stimulating factor (G-CSF). Grade 3 diarrhea occurred in one patient, necessitating a dose reduction of S1. Anorexia, rash, and nausea at grades 1 and 2 were commonly observed. The chemotherapy was finally discontinued in all 5 patients because of a deterioration in their PS in 2 patients, an intestinal obstruction caused by peritoneal dissemination in 1 patient, cholangitis in 1 patient, and diarrhea in 1 patient. The median duration of chemotherapy was 201 days (range: 14-360 days).

Survival after PTBD

All the patients eventually died; the median survival time (MST) after the execution of PTBD was 4.9 months (range: 0.7-15.4 months). The five patients who underwent chemotherapy demonstrated a significantly longer MST of 247 days, compared to the remaining 6 patients who had a MST of 62 days (P=0.0176; see Figure 1).

DISCUSSION

Metastatic lymphadenopathy along the hepatoduodenal ligament is common as a cause of obstructive jaundice after a gastrectomy for primary gastric cancer (7). Two-thirds of such lymph node metastases causing malignant biliary obstructions were reported to be derived from advanced cancers located in the gastric antrum, close to the hepatoduodenal ligament (7). In this review, the primary gastric cancer had spread in the antrum of the stomach in all but one of the patients, consistent with the findings of the previous report (7). Several other characteristics of the primary tumor demonstrated in this review, such as an ulcerative-type morphology, a diffuse-type histology, and transmural invasion, were also commonly observed in the previous report (7).

In our series, all the patients underwent initial PTBD without experiencing any major complications, such as hemorrhage, shock, or acute pancreatitis. During the follow-up period after PTBD, various complications can occur, including twisting, fracture, obstruction, or dislocation of the inserted tube as well as cholangitis (8-15). Eventually, 8 of the 11 patients developed transient cholangitis, and three patients developed tube obstructions that demanded a tube exchange.

PTBD improved various symptoms caused by obstructive jaundice, as shown in Table 2, and improved the patients' quality of life (QOL) though it might be possible to say that PTBD tube itself deteriorated the patients' QOL. General fatigue persisted in 3 of the 11 patients, which is generally considered to be a difficult symptom to eradicate by using only PTBD (16).

Chemotherapy may be contraindicated in patients with malignant biliary obstructions because the chemotherapeutic agents are maintained in the body at a high serum concentration, possibly resulting in a high incidence of adverse effects. Therefore, effective biliary drainage is essential for enabling chemotherapy to be performed safely, thereby improving patient prognosis. In the present series, 5 patients received chemotherapy after the effective relief of their jaundice using PTBD. Grade 4 neutropenia was observed in two patients, and grade 3 diarrhea was observed in one, while any clinical factors such as age, the level of serum T-bil either before or after PTBD, and the duration of jaundice, were not associated with the incidence of adverse effects of chemotherapy. These findings suggest that PTBD does not always guarantee the safety of chemotherapy, even after jaundice has been effectively relieved.

The MST of patients with obstructive jaundice

TABLE 2 Improvement in Symptoms after PTBD

Type of symptom	Number of patients				
	Initial	Disappeared	Improved	Persisted	Deteriorated
Generalized fatigue	8	2	3	3	0
Anorexia	7	0	7	0	0
Skin itching	4	3	1	0	0
Nausea	2	1	1	0	0
Abdominal fullness	2	0	1	1	0
Abdominal pain	1	0	1	0	0
Fever	1	1	0	0	0

TABLE 3 Clinical Characteristics of Patients who Did or Did Not Receive Chemotherapy

	chemo(+) n=5	chemo(-) n=6	*P* value
Male:Female	3:02	5:01	0.546
Mean age (years)	60.8	59.5	0.784
Mean lowest serum T-bil level after PTBD (mg/dL)	0.96	3.03	p=0.029
PS 0 or 1	4	2	0.242
H (+)	3	3	>0.999
P (+)	1	3	0.242

PS: performance status, H: liver metastasis, P: peritoneal metastasis, T-bil: total bilirubin, PTBD: percutaneous transhepatic biliary drainage.

caused by the local recurrence of gastric cancer has been reported to be 2.0-4.2 months, if the patients had received external biliary drainage alone (3,4). On the other hand, chemoradiotherapy (combining external radiation with cisplatin and 5-FU) after PTBD enabled a prolonged survival period of 14.4 months (17). In our series, the 5 patients who received chemotherapy had a significantly longer MST of 247 days, compared with the other patients who received external drainage alone (**Figure 1**). These findings may suggest a possibility that active treatment in addition to biliary drainage improve the prognosis of patients. However, there seemed to be many other factors affecting these survival differences between the patients with and without chemotherapy. Clinical background imbalance of PS, presence of peritoneal metastasis, or the mean serum T-bil level, as shown in **Table 3**, might be a cause of these differences. In addition, the number of estimated case in our series was too small to obtain a definitive conclusion regarding the significance of additional active treatment after PTBD.

In conclusion, PTBD was conducted safely and improved the QOL of patients with obstructive jaundice caused by the local recurrence of gastric cancer. Furthermore, the use of chemotherapy after PTBD might prolong patient survival although RCT study should be performed to assess the precise effect of chemotherapy after PTBD.

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World J Surg (2009) 33:290–295
DOI 10.1007/s00268-008-9828-x

World Journal of Surgery

Randomized Controlled Trial of Roux-en-Y Versus Rho-Shaped-Roux-en-Y Reconstruction After Distal Gastrectomy for Gastric Cancer

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Published online: 21 November 2008

Abstract

Background The main advantage of the Roux-en-Y (RY) operation is that it prevents bile and pancreatic juice from reaching the gastric mucosa, although the gastrojejunostomy may cause functional delayed gastric emptying (DGE), known as RY stasis syndrome. Rho-shaped Roux-en-Y reconstruction (rRY), an RY reconstruction with a rho-shaped anastomosis, is an established operation that has been found to be effective in preventing DGE.

Methods We conducted the randomized trial of RY versus rRY reconstruction after gastric cancer resection. The primary endpoint was the frequency of DGE, and secondary endpoints were the length of postoperative hospital stay, morbidity, and nutritional status. Seventy patients were enrolled, with 35 in each group.

Results The incidences of postoperative mortality and morbidity did not differ significantly between the two groups. There were no significant differences in nutritional status between the two groups after discharge. Delayed gastric emptying occurred in two patients (6%) in the RY group and four patients (11%) in the rRY group ($P = 0.67$). Logistic regression analysis revealed that truncal vagotomy was significantly associated with DGE inhibition.

Conclusions Our findings showed that RY reconstruction after gastrectomy may be as simple and sufficient as conventional reconstruction.

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Introduction

Roux-en-Y (RY) reconstruction of gastrojejunal continuity is an established means of draining the gastric remnant after distal gastrectomy. The RY operation is reported to be superior to the conventional Billroth I and Billroth II (BI and BII) reconstructions in preventing bile reflux into the gastric remnant and in impeding gastritis [1, 2]. In addition, the RY operation is superior in preventing carcinoma of the remnant stomach [3], although the gastrojejunostomy may cause delayed gastric emptying (DGE), known as RY stasis syndrome [4–8], with functional obstruction of the Roux limb. This syndrome is diagnosed based on clinical criteria, including epigastric fullness, postprandial pain, nausea, and vomiting of food. The prevalence of this syndrome has ranged from 10% to 20%, and the factors responsible for its development are still not well known. In recent years, RY reconstructions have been used frequently after gastrectomy for gastric cancer, and DGE has thus sometimes been observed. Once it occurs, quality of life (QOL) is reduced and hospital stay is prolonged. Thus DGE after gastrectomy may be a disadvantage for both the patients and the hospitals.

Separation of the Roux limb from the small intestinal pacemaker located in the duodenum allows ectopic pacemakers to arise in the Roux limb. These pacemakers, which appear in the limb some centimeters distal to its proximal end, drive the contractions of the proximal part of the limb in a reverse or oral direction toward the stomach. This creates stasis in the Roux limb and slows gastric emptying.

Some surgical methods, such as uncut RY reconstruction and rho-shaped RY reconstruction (rRY), have been reported or deduced to be effective in preventing RY syndrome [9–11]. In the rRY reconstruction, the ectopic pacemaker of the Roux limb may be located at the top of

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

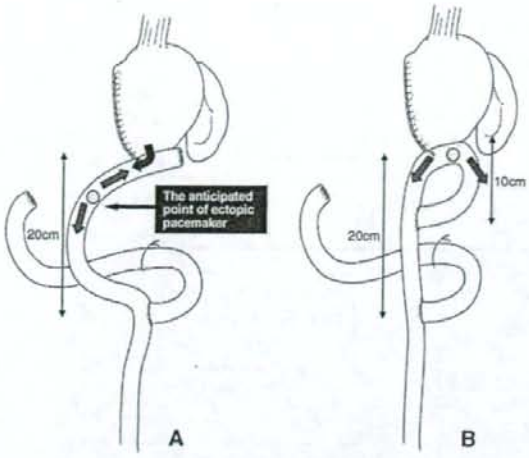

Fig. 1 Scheme of the conventional RY reconstruction (a) and rho-shaped RY reconstruction (b)

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

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

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).

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:

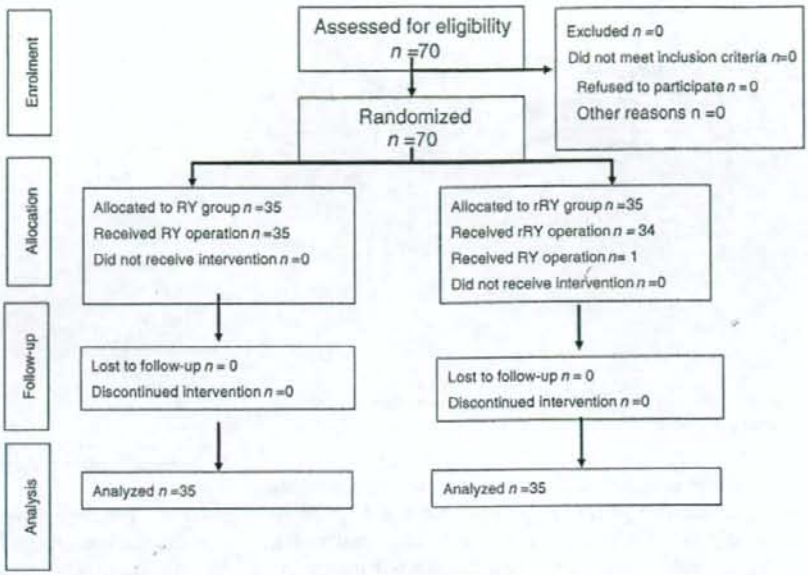

Fig. 2 CONSORT flow chart [27]

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
Abdominal 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.