Phase II trial of preoperative S-1 plus cisplatin followed by surgery for initially unresectable locally advanced gastric cancer

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Abstract

Background: The aim of this study was to evaluate the efficacy and feasibility of preoperative chemotherapy with S-1 plus cisplatin in patients with initially unresectable locally advanced gastric cancer.

Methods: We enrolled patients with initially unresectable locally advanced gastric cancer because of severe lymph node metastases or invasion of adjacent structures. Preoperative chemotherapy consisted of S-1 at 80 mg/m^2 divided in two daily doses for 21 days and cisplatin at 60 mg/m^2 intravenously on day 8, repeated every 35 days. If a tumor decreased in size, patients received 1 or 2 more courses. Surgery involved radical resection with D2 lymphadenectomy.

Results: Between December 2000 and December 2007, 27 patients were enrolled on the study. No CR was obtained, but PR was seen in 17 cases, and the response rate was 63.0%. Thirteen patients (48.1%) had R0 resections. There were no treatment related deaths. The median overall survival time (MST) and the 3-year overall survival (OS) of all patients were 31.4 months and 31.0%, respectively. Among the 13 patients who underwent curative resection, the median disease-free survival (DFS) and the 3-year DFS were 17.4 months and 23.1%, respectively. The MST and the 3-year OS were 50.1 months and 53.8%, respectively. The most common site of initial recurrence after the R0 resection was the para-aortic lymph nodes.

Conclusions: Preoperative S-1 plus cisplatin can be safely delivered to patients undergoing radical gastrectomy. This regimen is promising as neoadjuvant chemotherapy for resectable gastric cancer. For initially unresectable locally advanced gastric cancer, new trials using more effective regimens along with extended lymph node dissection are necessary.
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Keywords: Neoadjuvant chemotherapy; Lymph node dissection; Bulky lymph node; TS-1; Cisplatin; Para-aortic lymph node

Introduction

Gastric cancer is still one of the most common cancers in the world; 876,000 new cases were anticipated worldwide in the year 2000.[1] In Japan, 110,323 new cases were anticipated in the year 2003 and the 5-year survival rate of gastric cancer diagnosed from 1993 to 1996 was 54.4%.[2,3]

Currently, surgery remains the mainstay of curative treatment. However, only an R0 resection is associated with significant cure rates. Patients having microscopic (R1) or macroscopic (R2) residual tumor have an extremely poor prognosis.[4]

Preoperative and neoadjuvant chemotherapy represent investigational options. The rationale of preoperative chemotherapy is based on the difficulty of performing an R0 resection in patients with initially unresectable locally advanced tumors and the high risk of micrometastatic disease in these patients. Neoadjuvant chemotherapy has potential for resectable gastric cancer for the purpose of treating micrometastases.

Intensive chemotherapy is necessary for the improvement of the R0 resection rate and complete elimination of the micrometastases. However, it is difficult for patients who undergo gastrectomy to tolerate intensive chemotherapy. Because weight decreases by gastrectomy, it is necessary to reduce the dose of chemotherapy. The tolerance to chemotherapeutic agents with digestive organ toxicity was often reduced by gastrectomy-related gastrointestinal effects.

S-1 (TS-1, Taiho Pharmaceutical, Tokyo, Japan) is an orally active combination of tegafur (a prodrug that is converted by cells to fluorouracil), gimeracil (an inhibitor of dihydropyrimidine dehydrogenase, which degrades fluorouracil), and oteracil (which inhibits the phosphorylation of fluorouracil in the gastrointestinal tract, thereby reducing the gastrointestinal toxic effects of fluorouracil) at a molar ratio of 1:0.4:1. The response rate of S-1 alone exceeded 40% in two phase 2 trials involving patients with metastatic gastric cancer.[5,6] The combination chemotherapy of S-1 plus cisplatin (CDDP) achieved a high response rate (74%, 95%CI: 54.9—90.6) in a previous phase I/II study of patients with metastatic gastric cancer.[7]

These factors led us to perform the current phase II trial to investigate the use of an active preoperative chemotherapy regimen. The primary objectives of the trial were to investigate tolerance to the preoperative regimen, its effects on operative morbidity and mortality, and the response rate. Secondary objectives included evaluation of the R0 resection rate, disease-free and overall survival, and failure pattern.

Patients and methods

Patients

The study was conducted as a prospective multi-institutional phase II trial by the Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG) in Japan. All patients had histologically confirmed adenocarcinoma of the stomach. They also had to have initially unresectable locally advanced tumors because of invasion to adjacent structures or severe lymph node metastases, staged by contrast-enhanced CT as T2-3N2-3M0 or T4NanyM0, according to the Japanese Classification of Gastric Carcinoma (2nd English Edition).[8] They also had to have lymph node metastases that were measurable according to the RECIST[1.0] guidelines.[9] We did not require laparoscopic staging as an entry criterion for this study. Any sites of

suspected M1 disease had to be ruled out prior to entrance into the study. No prior chemotherapy or radiation was allowed. The age range was 20—75 years. The performance status (ECOG) was 0 from 1.

Because of the worse prognosis of type IV gastric cancer, also known as scirrhous or linitis plastica, we excluded such cases.[10] Acceptable hematologic profile (WBC $\geq$ 4000 cells/mm^3, hemoglobin $\geq$ 8.0 g/dl, platelets $\geq$ 100,000 cells/mm^3), and renal (BUN $\leq$ 25 mg/dl, creatinine $\leq$ 1.2 mg/dl and/or creatinine clearance $>$ 60 ml/min) and hepatic function (total serum bilirubin $<$ 1.5 mg/dl) were required. In addition, certain respiratory function test results (ratio of the forced expiratory volume in one second $\geq$ 50%, PaO2 in room air $\geq$ 70 mmHg) were required criteria. No clinically significant auditory impairment was allowed. Patients with prior cancer diagnosed during the previous 5-year period (except for colon carcinoma *in situ*) were excluded. Other exclusion criteria included significant cardiac disease, pregnancy or serious infections. The protocol was reviewed and approved by the Institutional Review Board of each institution. All patients gave written informed consent.

Preoperative chemotherapy

Patients found to have locally advanced gastric cancer as defined above, received two cycles of S-1 plus cisplatin every 35 days. Preoperative chemotherapy consisted of S-1 at 80 mg/m^2 divided in two daily doses for 21 days and cisplatin at 60 mg/m^2 intravenously on day 8. Physical examination, abdominal CT scan and assessment of toxicity were performed prior to each cycle. The response measurement of the preoperative chemotherapy was carried out according to the RECIST$^{1.0}$ guidelines. Because it was preoperative chemotherapy, response was not confirmed at least 4 weeks apart. Toxicity was recorded and graded according to the National Cancer Institution Common Toxicity Criteria (NCI-CTC) version 2.0 scale. Operative complication was graded according to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE v4.0). If a tumor decreased in size, according to protocol criteria, we added 1 or 2 more courses. If curative resection was considered possible after planned chemotherapy, the patient had surgery. If curative resection was considered difficult, a further course of chemotherapy was added. The doses of both agents were attenuated for grade $\geq$3 toxicities, using standard reduction criteria.

Surgery

The surgery was planned for 3—6 weeks from the day of last administration of chemotherapy. Surgery involved a radical resection, the extent of which (total or distal gastrectomy) depended on the site of the primary tumor, with a D2 lymphadenectomy. We performed D2 or more dissection in patients with metastasis to N3 lymph nodes before chemotherapy. Spleen preservation in total gastrectomy procedure was entrusted to the decision of each clinician.

Patients in whom curative resection was impossible underwent palliative operation. The postoperative treatment was left to the decision of each physician.

Biostatistical considerations

The 3 primary end points of the study were as follows; 1) tolerance to preoperative chemotherapy, 2) operative morbidity and mortality, and 3) objective response rate (ORR). Secondary end points were R0 resection rate, failure pattern, and disease-free and overall survival. One of the primary end points was ORR. The number of patients to be enrolled was calculated at 24, which was required given the assumption that the 95% confidence interval (CI) would be ±20%, assuming an expected response rate of 60%. Finally, we set the number as 30 patients in consideration of disqualified patients. The early stopping criterion of the trial was 3 treatment related deaths. Analogous samples were used to estimate the response rate, R0 resection rate, operative morbidity and mortality, and incidence of treatment related grade 3–4 toxicity. Overall survival (OS) of all patients was calculated from the day of registration in the trial. OS and disease-free survival (DFS) of the patients who underwent R0 resections were calculated from the day of surgery. Survival distributions were estimated using the Kaplan–Meier method.

Follow-up

Following completion of chemotherapy and surgery, patients were followed at 3- monthly intervals until year 3. Thereafter, 6-month follow-up visits were performed. CT scans and appropriate blood studies were performed on the occasion of each evaluation.

Results

Patient population

Between December 2000 and December 2007, 27 patients with initially unresectable local advanced gastric cancer were enrolled into the study from 9 institutions. As shown in Table 1, the male to female ratio was 20:7. The median age was 63 years. As for the histologic type, 15 cases were undifferentiated (including signet ring cell carcinoma) and 11 cases were differentiated type. One case was classified as mucinous carcinoma. There were 3 cStage IIIa (11.1%) preoperatively, 8 cStage IIIb (29.6%), and 16 cStage IV (59.3%).

Preoperative chemotherapy

The median number of preoperative chemotherapy regimens was 3 courses. Grade 3–4 toxicities associated with preoperative S-1/CDDP are described in Table 2. Hematologic toxicity (Grade 3/4) was 7.4% and non-hematologic

Table 1
Patient characteristics (n = 27).

		Number	%
Age, years	Median (range)	63	(48–75)
Gender	Male	20	74.1
	Female	7	25.9
Histology	Differentiated	11	40.7
	Undifferentiated	15	55.6
	Other	1	3.7
Pretreatment cStage	T2N2M0 (IIIA)	3	11.1
	T3N2M0 (IIIB)	7	25.9
	T4N1M0 (IIIB)	1	3.7
	T2N3M0 (IV)	5	18.5
	T3N3M0 (IV)	6	22.2
	T4N2M0 (IV)	3	11.1
	T4N3M0 (IV)	2	7.4

toxicity (Grade 3/4) was 3.7%. Treatment was generally well tolerated and no chemotherapy-related deaths were observed. While there was no CR, there were 17 cases of PR and the response rate was 63.0% [95%CI: 42.4–80.6] (Table 2).

Operative outcome

All patients who were entered into this trial had initially unresectable tumors. Nine patients were diagnosed as being unresectable when chemotherapy was completed and did not undergo surgery. Eighteen patients (66.7%) underwent laparotomy (Table 3). Thirteen patients (48.1%) had R0 resections. Three patients (11.1%) underwent R1 surgery, because of positive results of peritoneal washing cytology. Two patients underwent simple laparotomy because of peritoneal metastases or unresectable local extension of metastatic lymph nodes. Postoperative complications are described in Table 3. The incidence of complications was 22.2%. One patient underwent operative intervention because of pancreatic leakage; however, there were no surgery-related deaths.

Table 2
Courses, responses and toxicities of preoperative chemotherapy.

				n	%
Courses	Median (range)			3	(1–9)
Response	CR			0	0.0
	PR			17	63.0
	SD			6	22.2
	PD			4	14.8
Toxicities		Grade1/2		Grade3/4	
		n	%	n	%
	Neutropenia	10	37.0	2	7.4
	Thrombocytopenia	3	11.1	1	3.7
	Hemoglobin	21	77.8	1	3.7
	Vomiting	7	25.9	1	3.7
	Nausea	13	48.1	1	3.7
	Diarrhea	4	14.8	1	3.7
	Anorexia	17	63.0	1	3.7
	Cerebral infarction	0	0	1	3.7
Treatment related death				0	0.0

Table 3
Operative outcome (n = 27).

			Number	%
No operation			9	33.3
Operation			18	66.7
		R0 resection	13	48.1
		R1 resection	3	11.1
		R2 resection	0	0
		Simple Laparotomy	2	22.2
Complications				
		None	14	77.8
		Pancreatic leak	3 (Grade 1: 2, Grade 4: 1)	16.7
		Lymphorrhea	1 (Grade 1)	5.6
		Anastomotic leak	0	0.0
Re-operation			1	5.6
Mortality			0	0.0

Seven of 9 patients who did not undergo surgery received 2nd-line chemotherapy (S-1: 3 patients, S-1/CPT-11: 2 patients, CPT-11/CDDP: 1 patient, Paclitaxel: 1 patient). Four of 5 patients who underwent R1-2 surgery received further chemotherapy (S-1/Paclitaxel: 2 patients, S-1: 1 patient, CPT-11/CDDP: 1 patient).

Overall survival of all patients

Only one patient was lost to follow-up at 8 months from the first day of preoperative chemotherapy, but all other patients were followed more than three years. The median overall survival time and the 3-year overall survival rate of all patients were 31.4 months and 31.0% [95%CI: 17.5—55.1], respectively.

DFS, OS, and first relapse site of patients who underwent R0 resection

Thirteen patients underwent R0 resection. The details of these patients are shown in Table 4. Twelve of these 13

patients (92.3%) achieved PR after preoperative chemotherapy. The median number of course of chemotherapy of these patients was 3 (2—5). Of these patients, only 2 patients (15.4%) underwent D2 plus para-aortic lymph node dissection (D3). Downstaging was observed in 11 patients (84.6%). Seven of 13 patients received postoperative adjuvant chemotherapy (S-1: 4 patients, S-1 plus CDDP: 1 patient, CPT-11: 1 patient, CPT-11/CDDP: 1 patient). To date, recurrence has been diagnosed in 10 patients. First relapse site of five of ten patients was para-aortic lymph nodes. The median disease-free survival time and the 3-year disease-free survival rate of the 13 patients were 17.4 months and 23.1% [95%CI: 8.6—62.3], respectively (Fig. 1A). The median overall survival time and the 3-year overall survival rate of the 13 patients were 50.1 months and 53.8% [95% CI: 32.6—89.1], respectively (Fig. 1B).

Discussion

The combination chemotherapy of S-1 plus cisplatin was chosen because it had achieved a high response rate of 74% (95%CI: 54.9—90.6) in previous phase I/II study of patients with metastatic gastric cancer. The incidences of severe (Grade 3/4) hematological and non-hematological toxicities were 15.8 and 26.3%, respectively.[7] A randomized controlled trial in Japan showed the superiority of S-1/cisplatin compared with S-1 monotherapy according to the response rate and survival for metastatic gastric cancer.[11] Therefore, S-1/cisplatin therapy is now the standard treatment for metastatic gastric cancer in Japan.

This multi-institutional phase II prospective trial of preoperative chemotherapy in initially unresectable locally advanced gastric cancer showed that preoperative chemotherapy using S-1/cisplatin was not only feasible but also achieved a high response rate. The overall response rate was 63.0% [95%CI: 42.4—80.6]. The incidence of grade 3/4 toxicities was less than 10% and treatment related

Table 4
Patients who underwent R0 resection.

No.	cStage	Course	Response	Gastrectomy	D	Combined resection	fStage	Nodes	First relapse
1	T3N2M0 (IIIB)	2	PR	Distal	D3	Liver, Gallbladder	T2N2M0 (IIIA)	4	None
2	T3N3M0 (IV)	3	PR	Total	D2	Spleen, Panc. (tail) Gallbladder	T2N2M0 (IIIA)	6	Brain
3	T3N2M0 (IIIB)	2	PR	Total	D2	Spleen	T2N2M0 (IIIA)	10	Lymph (para AO)
4	T3N2M0 (IIIB)	2	PR	Distal	D3	None	T2N2M0 (IIIA)	3	None
5	T3N2M0 (IIIB)	3	PR	Total	D1*	Liver	T2N0M0 (IB)	0	None
6	T2N2M0 (IIIA)	2	SD	Distal	D2	Panc. (head)	T4N3M0 (IV)	7	Peritoneum
7	T4N2M0 (IV)	3	PR	Total	D2	Spleen, Panc. (tail)	T3N2M0 (IIIB)	10	Lymph (para AO)
8	T2N3M0 (IV)	4	PR	Distal	D2	Gallbladder	T2N2M0 (IIIA)	1	Bone
9	T4N3M0 (IV)	3	PR	Distal	D2	None	T1N0M0 (IA)	0	Lung
10	T4N1M0 (IIIB)	3	PR	Total	D2	Spleen	T2N2M0 (IIIA)	4	Lymph (hepatic)
11	T2N3M0 (IV)	5	PR	Total	D1*	None	T2N3M0 (IV)	2	Lymph (para AO)
12	T2N2M0 (IIIA)	3	PR	Total	D1*	None	T2N0M0 (IB)	0	Lymph (para AO)
13	T3N2M0 (IIIB)	3	PR	Total	D1*	None	T2N2M0 (IIIA)	13	Lymph (para AO)

D1*: we performed almost D2 dissection, but it classified D1 dissection according to the Japanese classification of gastric carcinoma (2nd English edition), because of preserving spleen.
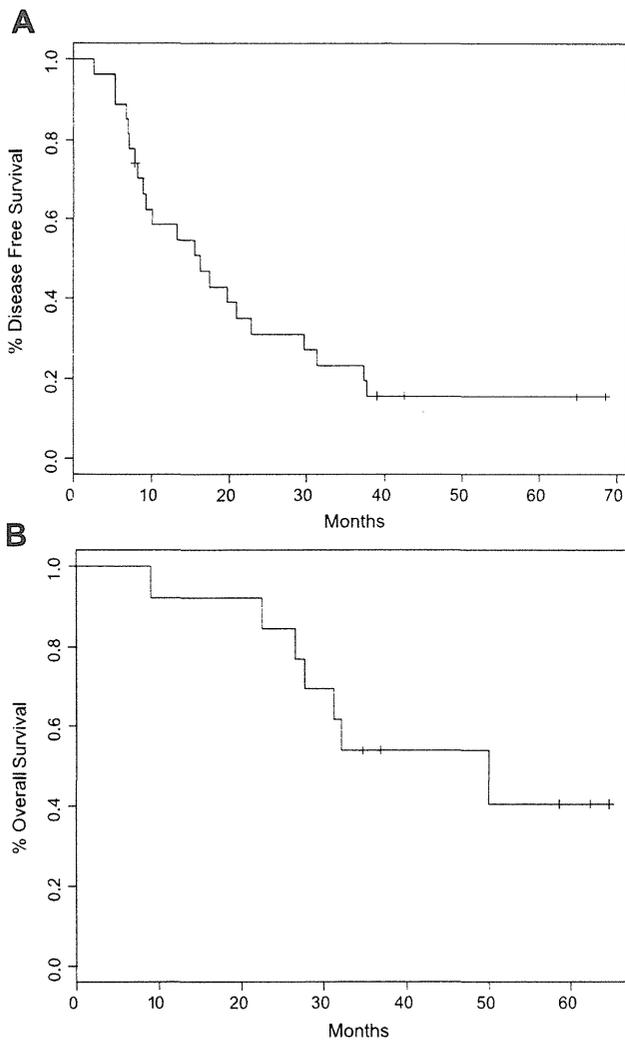
A

B

Figure 1. Disease-free and overall survival of the patients who underwent R0 surgery (n = 13).

mortality was 0.0%. Similar results were reported in other studies.[12,13] These results encourage the use of S-1/cisplatin combination chemotherapy as neoadjuvant treatment for patients who have resectable gastric cancer. Such trials are currently under way in Japan.[14,15]

The recently completed MAGIC trial constitutes a larger study regarding neoadjuvant chemotherapy in gastric cancer. In this study, 503 patients were randomized to three cycles of pre- and three cycles of postoperative epirubicin/cisplatin/5-FU (ECF) chemotherapy or surgery alone. Neoadjuvant chemotherapy was tolerable and was completed in 88% of patients. Significant downsizing (5.0 versus 3.1 cm median tumor size, $P < 0.001$), downstaging (54% versus 36% T1—T2 tumors, $P = 0.01$) and enhanced resectability (79% versus 69%, $P = 0.02$) were noted. Improved progression-free survival and survival were demonstrated, with an overall 5-year survival of 36% versus 23% for those undergoing surgery alone.[16] We should conduct phase III clinical trials of the

neoadjuvant chemotherapy of S-1/cisplatin therapy for resectable gastric cancer.

In Japan, the ACTS-GC trail demonstrated a survival advantage of postoperative adjuvant chemotherapy after R0 resection. R0 patients were randomized to adjuvant chemotherapy using S-1 (529 patients) versus surgery alone (530 patients); improved survival (3-year overall survival rates of 80.1% versus 70.1%, $P = 0.003$) was noted.[17] Adjuvant chemotherapy, as reported by the ACTS-GC Group, is now considered a standard treatment for R0 patients. However, of the 283 patients who had stage III disease and received S-1 adjuvant chemotherapy, 73 patients died. The hazard ratio of the adjuvant chemotherapy group worsened with an increasingly advanced stage. These results suggest that S-1 monotherapy is insufficient for patients who have stage III or more. However, for patients who have initially unresectable gastric cancer like the patients enrolled in this trial, S-1/cisplatin chemotherapy is insufficient because of the high relapse rate of patients who underwent R0 resection.

For the patients immediately after gastrectomy, highly toxic chemotherapy is difficult because of overlaps between chemotherapy-induced gastrointestinal toxicity and digestive symptoms due to gastrectomy.[18] Therefore, further improvements in preoperative therapy will require development of more effective chemotherapeutic regimens. During the last decade, several new agents with promising activity against gastric cancer were identified. These include paclitaxel, docetaxel, irinotecan and trastuzumab. These agents are now undergoing phase II and III trials, as part of combination regimens.[19—22] If improved outcome is seen in metastatic disease, these agents will undergo extensive testing in the preoperative setting.

The absence of laparoscopic staging might have allowed inclusion of patients with positive peritoneal cytology or small peritoneal implants that could have disappeared with the chemotherapy; these patients have a worse prognosis, which could have impacted on the final results. Actually, there were 3 cases of positive cytology at exploration after chemotherapy. Laparoscopic staging should be mandatorily included in future similar projects.

An interesting point is that there were many para-aortic lymph node recurrences in the patients who underwent R0 resection. Among 13 patients who underwent curative resection, initial recurrence in 5 patients was in a para-aortic lymph node. These patients had not undergone para-aortic lymph node dissection. The prognostic improvement effect of the para-aortic lymph node dissection was refuted by two clinical trials.[23,24] In the JCOG 9501 trial, 523 patients with resectable gastric cancer were enrolled, and 263 were assigned to D2 group and 260 were assigned to D2 plus para-aortic nodal dissection. The 5-year overall survival rate was 69.2% for D2 lymphadenectomy group and 70.3% for the D2 lymphadenectomy plus para-aortic nodal dissection group; the hazard ratio for death was 1.03 (95%CI, 0.77 to 1.37; $P = 0.85$). There were also no significant differences in recurrence-free

survival and the pattern of recurrence between the two groups.[23] In the East Asian Surgical Oncology Group trial, 269 patients with resectable gastric cancer were enrolled, and 135 were assigned to the D2 group and 134 were assigned to the D2 plus para-aortic nodal dissection. The 5-year overall survival rates were 52.6% for the D2 lymphadenectomy group and 55.0% for the D2 lymphadenectomy plus para-aortic nodal dissection group. There was no significant difference in survival between the two groups $(P = 0.801)$.[24] It was concluded that the D2 lymphadenectomy plus para-aortic nodal dissection did not improve prognosis regarding D2 lymph node dissection in the resectable gastric cancer.

However, in these trials, patients who had gross metastases to the para-aortic nodes were excluded. The incidence of metastases in the para-aortic nodes was lower than expected in 8.5% and 9.7%, respectively. The median number of metastatic nodes was only 2 nodes among the patients who underwent D2 plus para-aortic nodal dissection in the JCOG 9501. In the East Asian Surgical Oncology Group trial, the mean number of metastatic nodes was 5.9 in the para-aortic lymph node dissection group.

Recently, 15-year follow-up results of a randomized nationwide Dutch D1D2 trial were published. 711 patients underwent randomly assigned treatment with curative intent (380 in the D1 group and 331 in the D2 group). Overall 15-year survival was 21% for the D1 group and 29% for the D2 group. Gastric cancer-related death rate was significantly higher in the D1 group (48%, 182 patients) than that in the D2 group (37%, 123 patients). Local recurrence was 22% (82 patients) in the D1 group versus 12% (40 patients) in D2, and regional recurrence was 19% (73 patients) in D1 versus 13% (43 patients) in D2. After a median follow-up of 15 years, D2 lymphadenectomy was associated with lower locoregional recurrence and gastric cancer-related death rates than D1 surgery.[25] This difference was greater in the patients with lymph node metastases from 7 to 15.[26]

The observation period was shorter in the clinical trials of JCOG and East Asian Surgical Oncology Group than in the Dutch trail, and fewer mortality events occurred and also fewer metastases to lymph nodes. Therefore, para-aortic lymph node dissection might have better prognosis in patients with severe lymph node metastases like the patients enrolled in our trial.

In summary, preoperative S-1/cisplatin can be safely delivered to patients undergoing radical gastrectomy. The response rate was high, with no increase in operative morbidity and mortality compared with those upon surgery without preoperative chemotherapy.[27] Controlled trials of neoadjuvant chemotherapy using this regimen with the postoperative S-1 monotherapy for resectable gastric cancer are necessary. For initially unresectable locally advanced gastric cancer, the rate of recurrence was high, and the most common initial recurrent site was para-aortic lymph node. New trials, using a more effective regimen along with extended lymph node dissection are necessary.

Conflict of interest statement

The authors declare no conflict of interest.

Acknowledgments

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ORIGINAL ARTICLE

Overweight is a risk factor for surgical site infection following distal gastrectomy for gastric cancer

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Kentaro Inoue · Yutaka Kimura · Toshio Shimokawa · Hiroshi Furukawa ·
Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG)

Abstract

Background Our objective was to assess the risk factors for surgical site infections (SSIs) in gastric surgery using the results of the Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG) 0501 phase 3 trial.

Methods The OGSG 0501 trial was conducted to compare standard prophylactic antibiotic administration versus extended prophylactic antibiotic administration in 355 patients who underwent open distal gastrectomy for gastric cancer. Various risk factors associated with the incidence of SSI following gastrectomy were analyzed from the results of this multi-institutional randomized controlled trial.

Results Among the 355 patients, there were 24 SSIs, for an overall SSI rate of 7 %. Multivariate analysis using eight baseline factors (administration of antibiotics, age, sex, body mass index [BMI], prognostic nutritional index,

tumor stage, lymph node dissection, reconstructive method) identified that BMI ≥ 25 kg/m^2 was an independent risk factor for the occurrence of SSI (odds ratio 2.82; 95 % confidence interval [CI] 1.05–7.52; $P = 0.049$). BMI also showed significant relationships with the volume of blood loss and the operation time ($P = 0.001$ and $P < 0.001$, respectively).

Conclusion Compared with patients of normal weight, overweight patients had a significantly higher risk of SSI after distal gastrectomy for cancer.

Keywords Overweight · SSI · Gastric cancer · Gastrectomy · Obesity

Introduction

Surgical site infection (SSI) is one of the most common nosocomial infections, accounting for 14–16 % of nosocomial infections overall, and 38 % of nosocomial infections among surgical patients [1]. Previous studies on SSIs have provided feedback to surgeons and healthcare workers, and are important contributors to strategies for reducing the risk of SSI. Several studies concerning SSIs following gastric surgery have been conducted and reported. Prospective trials involving patients undergoing gastrointestinal surgery have reported some factors, such as overweight and hypo-albuminemia, which increase the risk of deep or organ SSI [2, 3].

Previously, we conducted a phase 3 randomized controlled trial (RCT), the Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG) 0501, to compare standard antimicrobial prophylaxis administration versus extended antimicrobial prophylaxis administration in patients receiving open distal gastrectomy for gastric

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cancer, and the results concerning the primary and secondary endpoints have been reported [4]. Because the OGSG 0501 trial was based on a single elective surgical procedure performed under uniform conditions, it is worthwhile to analyze the risk factors associated with SSIs following gastrectomy, using the data of the OGSG 0501.

Patients and methods

From June 2005 to December 2007, 355 gastric cancer patients underwent open distal gastrectomy under general anesthesia at multiple institutions. All 355 patients, 174 with Billroth-I reconstruction, 165 with Roux-en-Y reconstruction, and 16 with other methods of reconstruction following gastrectomy were included in the statistical analysis.

We defined SSI according to the surgical patient component of the 1999 Centers for Disease Control and Prevention (CDC) National Nosocomial Infection Surveillance (NNIS) System manual [1, 5, 6]; this definition includes superficial, deep, and organ/space SSIs. The patients were monitored for SSI according to the NNIS criteria until 30 days after the operation at each institution. The definitions of SSI are listed below [4, 5].

Superficial incisional SSI

Infection involves only skin or subcutaneous tissue of the incision and at least one of the following: purulent drainage, with or without laboratory confirmation, from the superficial incision; organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision; and at least one of the following signs of infection: pain or tenderness, localized swelling, redness or heat, and superficial incision that has been deliberately opened by the surgeon, unless the incision is culture-negative.

Deep incisional SSI

Infection involves deep soft tissues (e.g., fascial and muscle layers) of the incision and at least one of the following: purulent drainage from the deep incision but not from the organ or space component of the surgical site; a deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever (>38 °C localized pain, or tenderness, unless the site is culture-negative; or an abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathological or radiological examination.

Organ or space SSI

Infection involves any part of the anatomy (e.g., organs or spaces), other than the incision, which was opened or manipulated during an operation and at least one of the following: purulent drainage from a drain that is placed through a stab wound into the organ or space; organisms isolated from an aseptically obtained culture of fluid or tissue in the organ or space; or an abscess or other evidence of infection involving the organ or space that is found on direct examination, during reoperation, or by histopathological or radiological examination.

Risk factors considered in the present study included age, sex, body mass index (BMI), preoperative laboratory data (white blood cell number, lymphocyte number, albumin, and prognostic nutritional index [PNI]), gastric carcinoma stage, and operative characteristics (duration of surgery, operative blood loss, extent of lymph node dissection, operative curability, and method of reconstruction following gastrectomy). According to the World Health Organization classification, BMI ≥ 25 is considered as overweight and BMI <25 as non-overweight [7]. The operation and disease staging were performed according to the guidelines for clinical and pathologic studies in the 13th edition of the *Japanese classification of gastric carcinoma* [8]. PNI was calculated as follows: PNI = 10 × albumin (mg/dl) + 0.005 × lymphocyte number (cells/mm^3) [9]. There were no patients who underwent neoadjuvant chemotherapy.

Outline of OGSG 0501, as the original trial

The protocol for the prospective study OGSG 0501 was reviewed and approved by the ethics review board of each participating institution. Eligible patients at each institution participating in the Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG) provided written consent to participate in the trial, clinical follow up, and data collection. The OGSG 0501 was a multi-institutional RCT to evaluate the optimal duration of prophylactic antibiotic administration in patients initially planned to have distal gastrectomy with D2 lymphadenectomy for gastric cancer. Patients were randomly assigned to either the standard antibiotic prophylaxis group (standard group) or the extended prophylactic antibiotic group (extended group). The standard group received 1 g of cefazolin less than 30 min before the incision and every 3 h intraoperatively. The extended group received 2 g/day of cefazolin on postoperative days 1 and 2 in addition to receiving the same dose as that given to the standard group. The primary endpoint of OGSG 0501 was the incidence of SSIs. Analysis was based on the intention-to-treat principle. The

results concerning the endpoints and other details of the study design have been reported [4].

The OGSG 0501 trial was registered with the University Hospital Information Network (UMIN-CTR) (http://www.umin.ac.jp/ctr/) under identification number UMIN000000631.

Statistical analysis

All enrolled patients were divided into two groups according to whether or not they developed SSI postoperatively. All factors were compared between the two groups by univariate analysis, i.e., the χ^2 test or Fisher's exact test for categorical variables, or a two-sided Mann–Whitney U-test for continuous variables.

Multivariate analysis was also performed using a logistic regression model to assess the effects of the factors on SSI. A P value of <0.05 was considered to be statistically significant. Statistical analyses were performed with SPSS version 17.0 (SPSS Japan, Tokyo, Japan).

Results

There were 355 distal gastrectomies (176 patients in the standard group, 179 patients in the extended group) performed as inpatient procedures for gastric cancer (Fig. 1). The baseline patient and operative characteristics are shown in Table 1. The results concerning the detailed patient characteristics can be referred to in the previously reported data [4]

The overall SSI rate for open distal gastrectomy was 7 % (24/355), 5 % (8/176) for the standard group, and 9 % (16/179) for the extended group. Six patients had superficial type SSIs and 18 had organ/space type SSIs. There were no deep SSIs.

Univariate analysis of risk factors for SSI demonstrated that extended administration of antibiotics, male sex, BMI ≥ 25 kg/m^2, and duration of operation >200 min were associated with a higher, but non-significant, incidence of SSIs ($P = 0.105$, $P = 0.098$, $P = 0.158$, and $P = 0.076$, respectively). However, multivariate analysis revealed that only BMI ≥ 25 kg/m^2 was independently associated with an increase in the incidence of SSIs (odds ratio 2.82; 95 % confidence interval [CI] 1.05–7.52; $P = 0.049$) (Table 2). For the risk factors in the multivariate analysis, we included only the baseline factors, because if operative data, such as duration of operation and blood loss, had been added for the analysis, the results would have been confusing.

Subgroup analysis showed that surgery for the patients with BMI ≥ 25 resulted in a larger volume of blood loss and a longer duration of operation when compared with finding in patients with BMI <25 ($P = 0.001$ and $P < 0.001$, respectively) (Table 3).

The relationship between BMI and the type of SSI (superficial or organ/space) was not significant (Table 4).

Discussion

The present study focused on the risk factors for SSI. The risk of SSI after gastric surgery for gastric cancer was

Fig. 1 CONSORT flowchart of Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG) 0501 trial. *Administration* administration of antibiotics
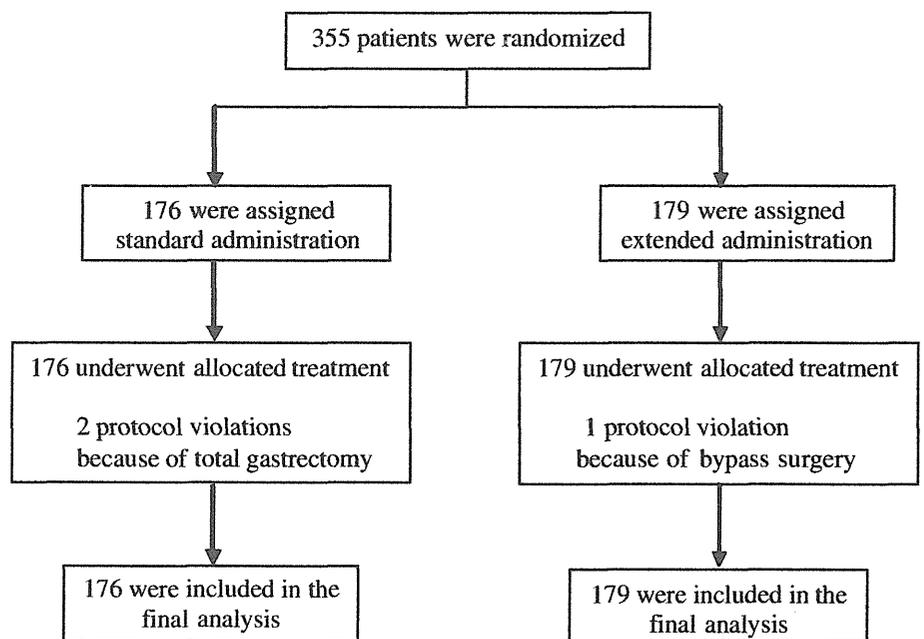
statistically evaluated using a logistic regression model. Our data suggest that the risk of SSI depends on whether the patient's BMI is less than 25 or 25 or greater.

Investigators have reported the overall SSI incidence for open distal gastrectomy to be in the range of 10–16 % [3, 10]. The incidence was 7 % in the present study. Watanabe et al. [10] reported a higher incidence of organ/space SSIs than superficial and deep incisional SSIs in gastric surgery.

However, many investigators have reported that colorectal surgery is more frequently associated with superficial incisional SSIs than with deep incisional or organ/space SSIs [10–12]. Complications specific to gastric surgery with lymphadenectomy, such as pancreatic fistula, may affect the incidence of organ/space SSIs. The difference in thickness between upper and lower abdominal subcutaneous tissues may also affect the incidence of various types of SSIs. In our study, the relationship between BMI and the type of SSI (superficial, deep, and organ/space) was not significant.

The impact of BMI on specific complications after elective abdominal or general surgery, especially colorectal surgery for cancer, has been assessed. SSI is the most common complication after colectomy, and obesity or overweight is thought to increase this risk by 2.5- to 5-fold as compared with patients of normal weight [13–16]. This risk may be related to the decreased oxygen tension in relatively avascular adipose tissue, differences in wound healing, greater wound size, or technical difficulties [13, 17]. However, another report suggests that obesity or overweight is not a risk factor for SSI after colectomy [18].

Recently, risk factors associated with SSI in upper gastrointestinal surgery have been reported. Watanabe et al. [10] reported that in upper alimentary tract surgery, significant relationships were observed between the incidence of SSI and both intraoperative blood loss and combined resection procedures, but BMI was not associated with the incidence of SSI. Imai et al. [19] found, in a retrospective study, that diabetic gastric surgery patients had a 2.7-fold higher risk of SSI as compared with the patients without diabetes, open surgery had a 1.9-fold higher risk of SSI as compared with laparoscopic surgery, and operations lasting for 6 h or longer had a 2.8-fold

Table 1 Baseline and operative characteristics of study patients ($n = 355$)

Age (years)[a]	65 (35–84)
Sex, male/female	240/115
BMI (kg/m^2)[a]	22.4 (12.4–33.0)
Stage IA/IB/II/IIIA/IIIB/IV	189/58/47/24/17/20
Antimicrobial prophylaxis administration	
Extended/standard	179/176
White blood cell number (cells/mm^3)[a]	5700 (2890–10800)
Lymphocyte number (cells/mm^3)[a]	1814 (510–4679)
Hemoglobin (mg/dl)[a]	13.4 (7.0–18.4)
Albumin (mg/dl)[a]	4.2 (2.0–5.3)
PNI[a,b]	51.42 (25.1–68.9)
Duration of surgery (min)[a]	204 (58–428)
Operative blood loss (ml)[a]	200 (0–1700)
Lymph node dissection D0/1/2/3	16/96/240/3
Curability R0–1/2	332/23
Reconstruction method BI/BII/RY/other	174/4/165/12

BMI body mass index, *BI* Billroth-I reconstruction, *BII* Billroth-II reconstruction, *RY* Roux-en-Y reconstruction

[a] Values are expressed as medians (ranges)

[b] PNI (prognostic nutritional index) was calculated as follows: PNI = 10 × albumin (mg/dl) + 0.005 × lymphocyte number (cells/mm^3)

Table 2 Univariate and multivariate analysis for the risk of SSI ($n = 355$)

	SSI present ($n = 24$)	SSI absent ($n = 331$)	Univariate logistic P value	Multivariate logistic Odds ratio (95 % CI)	Multivariate logistic P value
Extended administration of antibiotics	16	163	0.105	1.89 (0.72–4.93)	0.167
Age >65 years	14	173	0.566	1.15 (0.46–2.89)	0.535
Male sex	20	220	0.098	2.22 (0.69–7.09)	0.179
BMI ≥25 kg/m^2	8	69	0.158	2.82 (1.05–7.52)	0.049*
PNI >50	14	169	0.531	3.70 (0.61–22.7)	0.412
Stage >III	4	57	0.945	1.06 (0.29–3.88)	0.516
Lymph node dissection D2 or 3	16	227	0.846	1.08 (0.41–2.85)	0.885
Reconstruction BII or RY	13	156	0.506	1.33 (0.52–3.41)	0.528
Duration of surgery >200 min	17	171	0.076	–	
Operative bleeding >200 ml	15	174	0.349	–	

All factors in the two groups were compared by univariate analysis. Multivariate analysis was performed using a logistic regression model

CI confidence interval, *BII* Billroth-II reconstruction, *RY* Roux-en-Y reconstruction

* *P* value of <0.05 was considered to be statistically significant

Table 3 Relationship between overweight and surgical outcome (n = 355)

	BMI <25 (n = 278)	BMI ≥25 (n = 77)	P value
Operative blood loss (ml)			0.001*
<200	143 (51)	23 (30)	
≥200	135 (49)	54 (70)	
Operation time (min)			<0.001*
<200	147 (53)	20 (26)	
≥200	131 (47)	57 (74)	

Compared by χ^2 test. Values in parentheses are percentages

* P value of <0.05 was considered to be statistically significant

Table 4 Relationship between BMI and type of SSI (n = 24)

	BMI <25 (n = 16)	BMI ≥25 (n = 8)	P value
Type of SSI			0.317*
Superficial	3 (19)	3 (38)	
Organ/space	13 (81)	5 (62)	

Compared by χ^2 test. Values in parentheses are percentages

* P value of <0.05 was considered to be statistically significant

higher risk of SSI compared with shorter operations, but high BMI was not associated with the risk of SSI. On the other hand, a prospective trial found that among overweight and hypo-albuminemic patients undergoing gastrointestinal surgery, there was an increased risk of deep/organ SSI [2, 3]. The data from our present multivariate analysis suggested that BMI ≥25 kg/m^2 was independently associated with an increased incidence of SSI after distal gastrectomy for gastric cancer. However, other clinical baseline characteristics (such as PNI), operative characteristics (such as duration of surgery, operative blood loss, lymph node dissection, the method of reconstruction following gastrectomy), and the extended administration of antibiotics had no significant association with the incidence of SSI. Moreover, in our study, because surgery for overweight patients required more time and incurred a larger volume of blood loss, it appeared that the incidence of SSI for overweight patients was higher than that in patients of normal weight. Our data are comparatively reliable and noteworthy, because this study was derived from the data of a phase 3 prospective randomized trial that was based on a single elective surgical procedure performed under uniform conditions

In conclusion, the present study has revealed that, compared with patients of normal weight, overweight patients have a significantly higher risk of SSI after distal gastrectomy for cancer, and the SSIs in overweight patients may not be prevented by the extended administration of antibiotics. Quality improvement initiatives for overweight patients undergoing gastric surgery should focus on the complication of SSI.

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Long-term Outcome after Proximal Gastrectomy with Jejunal Interposition for Gastric Cancer Compared with Total Gastrectomy

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Abstract

Background Proximal gastrectomy (PG) has been widely accepted as treatment for early gastric cancer located in the upper third of the stomach. Reconstruction by jejunal interposition has been known to reduce reflux esophagitis for PG patients. The aim of this study was to compare the long-term outcomes of patients who underwent PG with jejunal interposition with those treated by total gastrectomy (TG).

Methods Data on 102 cases of PG with jejunal interposition and 49 cases of TG with Roux-Y reconstruction for gastric cancer were analyzed retrospectively in terms of overall survival, weight maintenance, anemia and nutritional status, and endoscopic findings.

Results Median follow-up time was 59 months in the both groups. There was no significant difference in the overall 5-year survival rate between the PG group (94 %) and the TG group (84 %). The PG group showed significantly better body weight maintenance at the first year. The laboratory blood tests showed that the PG group had a significantly better red blood cell count and hemoglobin and hematocrit levels at the second and third year. However, postoperative endoscopic surveillance detected reflux esophagitis (3 %), peptic ulcer (9 %), and metachronous gastric cancer (5 %) in the PG group.

Conclusions Proximal gastrectomy maintains comparable oncological radicality to TG and is preferred over TG in terms of preventing postoperative anemia. However, periodic endoscopic follow-up is necessary to monitor the upper gastrointestinal tract.

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Introduction

Gastric cancer is one of the most common types of solid tumor, and it is estimated to be the fourth most common in terms of morbidity and the second most frequent cause of cancer death in the world [1]. In recent years, the frequency of cancers in the upper third of the stomach has been increasing in both Western and Asian countries [2–4]. As a function-preserving operation for such lesions, proximal gastrectomy (PG) has been widely accepted because it maintains comparable oncological radicality to total gastrectomy (TG), the standard operation for the lesions [5–8]. Although reflux symptoms and esophagitis had been major postoperative problems for patients who underwent PG [9, 10], a sphincter-substituting reconstruction called "jejunal interposition" has minimized these symptoms and improved the long-term outcome [11–13]. There has been one meta-analysis [14] and several reports comparing the long-term outcomes of TG and those of PG with jejunal interposition [15, 16], PG with jejunal pouch interposition [17] and PG with esophagogastrostomy [5, 8, 16, 18]. Because these reports differ in their conclusions, it remains controversial whether PG provides a better long-term outcome than TG. We conducted a large-scale comparison study with the aim of clarifying the long-term outcome of PG with jejunal interposition by comparing it to that of TG with Roux-Y reconstruction in terms of overall survival, weight maintenance, anemia and nutritional status, and endoscopic findings.

Patients and methods

All clinical diagnoses and pathological examinations of the resected specimens in this study were classified according

to AJCC/UICC cancer staging guidelines (7th ed.) [19]. The indication for PG in our institute is gastric cancer located in the upper third [20] of the stomach with it clinically staged as T1-2N0M0. The techniques for PG with jejunal interposition have already been described [11]. From January 1999 to December 2008, we performed PG with jejunal interposition on 107 patients with gastric cancer at the Shikoku Cancer Center and experienced no postoperative deaths (Fig. 1). None of these patients had prophylactic cholecystectomy or other combined resections. From this PG group, we selected 102 patients for this study who underwent postoperative surveillance at the Shikoku Cancer Center for more than 1 year.

We compared the long-term outcomes after PG to outcomes seen after TG. In the same period (1999–2008), there were 321 cases of TG performed for gastric cancer at the Shikoku Cancer Center. From this group we selected the 51 patients who were clinically diagnosed as having T1-2N0M0 gastric cancer [19] and underwent TG with Roux-Y reconstruction. Although most of these TG patients underwent prophylactic cholecystectomy, no other combined resection such as splenectomy was carried out in these patients. The final selection criteria involved those who underwent postoperative surveillance at the Shikoku Cancer Center for more than 1 year, resulting in 49 TG patients (Fig. 1).

R0 resection was achieved for all patients in this study. Following surgery, prophylactic antireflux medications such as camostat mesilate, H2-blocker, or proton pump inhibitor were not given to any patient. Prophylactic anti-anemia medication such as a vitamin B12 injection or oral iron supplements was also not administered to any patient. The patients underwent laboratory examinations, chest X-rays, and CT scans every 6 months. Surveillance by upper endoscopy was done annually for PG patients and every 2–3 years for TG patients. In surveillance endoscopy, the reflux esophagitis was graded using the Los Angeles classification system [21]. The patients with residual food grade ≥ 3 by the RGB classification [22]

were diagnosed as having residual food. The definition for metachronous gastric cancer in the remnant stomach was described previously [23]. The red blood cell count, hemoglobin level, and hematocrit level were used as indicators of postoperative anemia. Total protein, serum albumin, and total cholesterol were used as indicators of postoperative nutritional status.

JMP 9 statistical software (SAS Institute, Inc., Cary, NC, USA) was used for all statistical analyses. The overall survival was calculated by the Kaplan–Meier method and analyzed by the log-rank test. Pearson's χ^2 test or Wilcoxon test was used to compare the two groups. The level of significance was set at $p < 0.05$.

Results

The characteristics of the groups are given in Table 1. The age and sex distribution were similar in the two groups. Although a less extensive lymphadenectomy was carried out during the operation in the PG group, there was no significant difference between the two groups. Vagal nerve preservation was carried out in 75 PG patients (74 %), while no patients underwent vagal preservation in TG group. Tumor size was significantly larger in the resected specimen in the TG group, and the TG group had significantly more cases with undifferentiated type cancer upon histological examination. In the pathological examination, a significantly more advanced T factor and stage were seen in the TG group.

After median follow-up periods of 59 months (range = 12–147) in the PG group and 59 months (range = 14–116) in the TG group, there have been nine deaths in the PG group and eight deaths in the TG group. Figure 2 shows the overall survival curves for both groups. The 5-year survival rate was 94 % for the PG group and 84 % for the TG group, and the log-rank test showed no significant difference between the two groups. In the PG group, two patients died from cancer recurrence, two patients died from cancers other than gastric cancer, three patients died from benign disease, and two patients died from unknown causes. In the TG group, six patients died from cancer recurrence, one patient died from cancers other than gastric cancer, and one patient died from benign disease.

The PG group showed better body weight maintenance until the third year, with the difference during the first year being statistically significant (Fig. 3). The percent preoperative body weight at the third year was 88 % in the PG group and 86 % in the TG group and was not significantly different between the two groups.

In the postoperative laboratory examination of blood, we used the red blood cell count, hemoglobin level, and
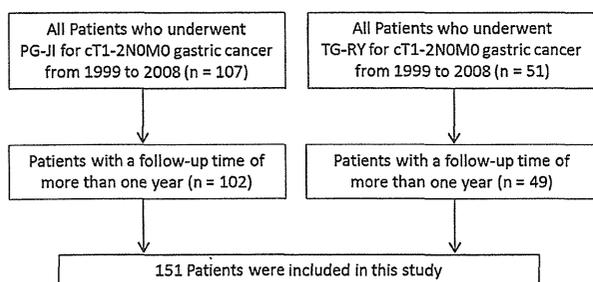
Fig. 1 Study design. *PG-JI* proximal gastrectomy with jejunal interposition, *TG-RY* total gastrectomy with Roux-Y reconstruction. Staging was classified according to the 7th edition of AJCC/UICC cancer staging system [19]

Table 1 Characteristics of the patients

Characteristics	Proximal (102)	Total (49)	p value
Age [median (range)] (years)	67 (44–85)	71 (34–86)	0.391[c]
Sex [No. (%)]			0.591[d]
Male	79 (77)	36 (73)	
Female	23 (23)	13 (27)	
Lymphadenectomy[a] [No. (%)]			0.053[d]
D1	15 (15)	2 (4)	
D1+/D2	87 (85)	47 (96)	
Tumor size [median (range)] (mm)	25 (5–100)	50 (7–210)	< 0.001[c]
Histological Grade[b] [No. (%)]			0.025[d]
G1/G2 (differentiated)	73 (72)	26 (53)	
G3/G4 (undifferentiated)	29 (28)	23 (47)	
Pathological T factor[b] [No. (%)]			0.007[d]
pT1	83 (81)	30 (61)	
pT2	8 (8)	9 (19)	
pT3	10 (10)	5 (10)	
pT4a	1 (1)	5 (10)	
Pathological N factor[b] [No. (%)]			0.086[d]
pN0	90 (88)	35 (72)	
pN1	6 (6)	7 (14)	
pN2	4 (4)	5 (10)	
pN3	2 (2)	2 (4)	
Pathological stage[b] [No. (%)]			0.040[d]
IA	77 (75)	24 (50)	
IB	12 (12)	10 (20)	
IIA/IIB	8 (8)	10 (20)	
IIIA/IIIB/IIIC	5 (5)	5 (10)	

[a] According to Japanese gastric cancer treatment guidelines 2010 (ver. 3) [31]

[b] According to AJCC/UICC 7th edition [19]

[c] Wilcoxon test

[d] Pearson's χ^2 test

Fig. 2 The overall survival curves after proximal and total gastrectomy. There is no significant difference between the two groups by the log-rank test ($p = 0.189$). PG proximal gastrectomy (*black line*), TG total gastrectomy (*gray line*)

Fig. 3 The percentage of postoperative body weight to the preoperative. Data are expressed as mean ± standard deviation. PG proximal gastrectomy (*black line*), TG total gastrectomy (*gray line*). *$p = 0.034$

hematocrit level as an indicator of anemia. The three indicators gradually dropped in the TG group after the operation. In contrast, they were well maintained in the PG group until the third year. All three indicators were significantly higher in the PG group at the second and third year (Fig. 4). In blood chemistry tests, we used the level of total protein, serum albumin, and total cholesterol as an indicator of postoperative nutritional status (Fig. 5). We did not see any significant difference between the two groups at any time point.

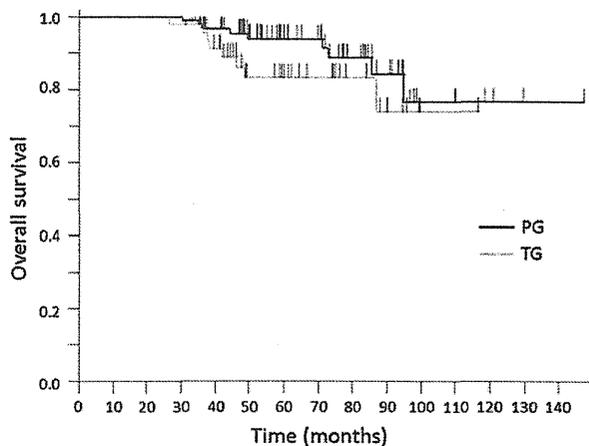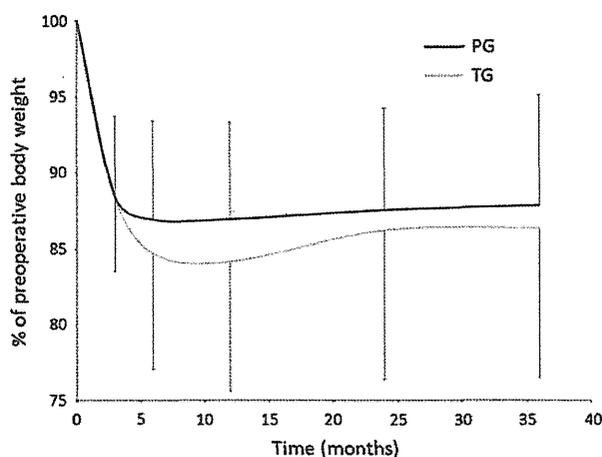Ninety-five patients in the PG group and 44 patients in the TG group underwent upper endoscopic postoperative surveillance at least one time (Table 2). The frequency of the examination was significantly greater in the PG group. Reflux esophagitis was observed in three PG patients and in one TG patient. There was no significant difference between the two groups. Nine patients (9 %) in the PG group were diagnosed as having a peptic ulcer in the reconstructed jejunum and/or gastric remnant. In contrast, the examination detected no peptic ulcers in the reconstructed jejunum in the TG group. The difference between the two groups was statistically significant. The typical image of the peptic ulcer is shown in Fig. 6. Peptic ulcers formed at the interposed jejunum near the jejunogastrostomy. All patients with peptic ulcers were medicated with H2-blocker or proton pump inhibitor and all were cured following treatment. Endoscopic

beyond our preoperative diagnosis. Since PG is accepted as a function-preserving operation for gastric cancer at a relatively early pathological stage, the preoperative diagnostic accuracy should be improved in the future.

Weight maintenance

In this study, the PG group had a significant advantage in body weight maintenance at the first year. However, this advantage was lost by the second and third year when the body weight of the TG group recovered. We speculate that the difference in body weight maintenance is because of the limited reservoir function in PG with jejunal interposition. It has been reported that PG with jejunal pouch interposition showed significantly better weight maintenance than TG from the first to the third year [17]. PG with jejunal pouch interposition may have some advantage with respect to weight maintenance because reports indicate that this technique supports reservoir function and yields nutritional advantages [24–26].

Postoperative anemia and nutritional status

In this study, PG was preferred over TG in terms of preventing postoperative anemia because red blood cell count, hemoglobin, and hematocrit measurements in the TG group gradually dropped by the third year, while the levels in the PG group were well maintained (Fig. 4). These results are consistent with those of previous reports [8, 17]. One of the causes for the postoperative anemia after TG has been vitamin B12 malabsorption [27, 28]. Since one study [17] reported that serum vitamin B12 levels were significantly better in the PG group than in the TG group at the second and third year, the remnant distal stomach after PG may play an important role in preventing vitamin B12 malabsorption.

Endoscopic findings

In this study, a wide range of remnant gastric comorbidity was seen during surveillance endoscopy in PG patients (Table 2). We observed peptic ulcer formation in nine PG patients. Likewise, several previous studies reported peptic ulcers in the interposed jejunum and remnant stomach after PG [12, 15, 29]. Gastric acid secretion remains in the gastric remnant after PG, so patients should be monitored closely in the follow-up period. Once an ulcer is detected, antisecretion medication such as an H2-blocker or proton pump inhibitor are recommended. Treatment with these drugs cured all patients with peptic ulcers in this study.

In our last two studies [23, 30], we reported that the gastric remnant after PG showed a higher incidence of metachronous cancer. In this study, five PG patients were diagnosed as having metachronous cancer in the gastric remnant. Since the median period between the primary surgery and detection of the metachronous cancer was 50 months (range = 34–101), we recommend long-term surveillance endoscopy to detect such lesions at an early stage.

It has been reported that jejunal interposition improved reflux esophagitis for PG patients when compared to esophagogastrostomy [12, 13]. The reported incidence of reflux esophagitis of 1.7–5.0 % [12, 13] is comparable to our result (3.2 %). This surgical technique lowers reflux because the interposed jejunum served as a sphincter-substituting reconstruction. In this study, the median length of the interposed jejunum was 12 cm (measured intraoperatively, range = 8–20). That was short enough for the endoscope to reach the remnant stomach in all surveyed patients. However, a moderate amount of residual food was observed in 30 % of PG patients in this study, which hindered observation of the entire surface, even with body rolling (grade 3 or worse by RGB classification [22]). All of the patients needed reexamination later. In order to observe the entire surface of the remnant stomach and detect any suspicious lesions or changes at the examination effectively, a full liquid diet may be recommended for the day before the examination.

In conclusion, PG showed comparable oncological radicality to TG. PG is preferred over TG in terms of prevention of postoperative anemia. However, periodic upper endoscopic follow-up is necessary to monitor the upper gastrointestinal tract. PG is not recommended at a hospital that cannot perform the surveillance endoscopy, otherwise the remnant stomach may cause critical comorbidity in PG patients.

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HOW TO DO IT

A new technique for resecting gastric remnant cancer after proximal gastrectomy with jejunal interposition

Isao Nozaki · Shinji Hato · Akira Kurita

Abstract Surgery for gastric remnant cancer after distal gastrectomy is well established; however, little is known about the removal of remnant gastric cancer following proximal gastrectomy with jejunal interposition. We introduce a surgical technique for removing remnant cancer under these circumstances. We used this technique to remove a total gastric remnant with radical lymph node dissection, while preserving the interposed jejunum for easy re-reconstruction by Roux-en-Y anastomosis, in five patients. The median operating time was 199 min and the median blood loss was 330 ml. There were no postoperative deaths or major complications and all five patients were discharged within 14 days after surgery. Our technique for total resection of the gastric remnant after proximal gastrectomy and re-reconstruction with preserved interposed jejunum is easy, safe, and effective.

Keywords Surgical technique · Proximal gastrectomy Gastric stump cancer

Introduction

Proximal gastrectomy is performed widely as a function-preserving operation for early gastric cancer located in the upper third of the stomach because it maintains comparable oncological radicality to total gastrectomy for such lesions [1–4]. To overcome the reflux symptoms and esophagitis that can develop after proximal gastrectomy, a sphincter-substituting reconstruction called 'jejunal interposition' was devised, which has minimized these symptoms and improved postoperative quality of life [2, 5]. With proximal gastrectomy becoming a standard procedure, the incidence of remnant cancer after proximal gastrectomy is increasing [6–9]. Total resection of the gastric remnant with radical lymph node dissection is the best choice for resecting the cancer curatively, if endoscopic mucosal resection is not indicated, although gastric remnant resection may be difficult when the proximal gastrectomy involved reconstruction with jejunal interposition. We have encountered five such cases since we started performing proximal gastrectomy with jejunal interposition. We describe our technique of resection under these circumstances and report the perioperative outcomes of these five patients.

Methods

The techniques of proximal gastrectomy for gastric cancer with jejunal interposition have been described [1]. Briefly, when we perform this procedure, we preserve half to two-thirds of the distal stomach and excise the lymph nodes from stations #1, 2, 3, 4s, 7, 9, 11p, and 11d, leaving those from stations #4d, 5, and 6 [10]. The jejunal interposition is about 15 cm long and the marginal arteries on both the oral and anal side of the interposed jejunum are divided for easy mobilization (Fig. 1a). The operation that we describe here consists of total resection of the gastric remnant with lymph node dissection and preservation of the interposed jejunum for easy re-reconstruction. The right gastric vessels and right gastroepiploic vessels are divided at their roots, which completes dissection of perigastric lymph nodes such as stations #4d, 5, and 6. We use a linear stapler to transect the duodenum at the anal side of the pyloric ring

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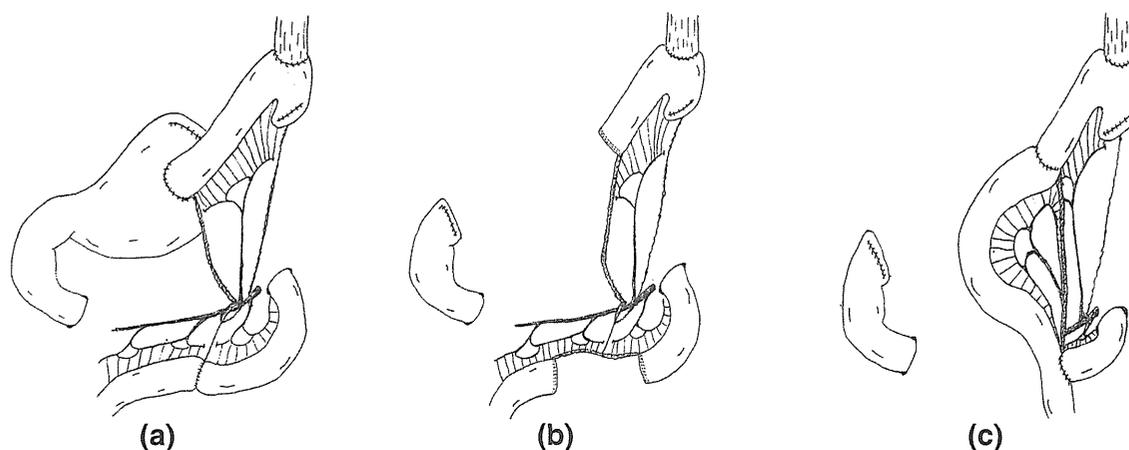160 Minami-umemoto, Matsuyama 791-0280, Japan
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Fig. 1 a Typical image of completed proximal gastrectomy with reconstruction by jejunal interposition in this institution. **b** Resection of the total gastric remnant with preservation of the interposed jejunum and sacrifice of the jejunal section containing the old jejunojejunostomy for easy mobilization. **c** Re-reconstruction by Roux-en-Y anastomosis

Fig. 2 Intraoperative picture and its schema after re-reconstruction. *ESO* Esophagus, *IJ* interposed jejunum, *RYL* Roux-en-Y limb, *PJ* Proximal jejunum
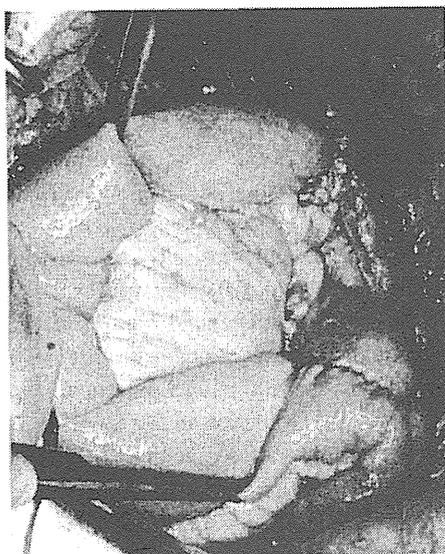
and to transect the interposed jejunum, 5 cm from the jejunogastrostomy. This preserves 10 cm of proximal interposed jejunum (Fig. 1b). Approximately 10 cm of jejunum, which includes the jejunojejunostomy from the previous surgery, is sacrificed to extend the jejunal pedicle for easy mobilization. A new anastomosis between the antecolic Roux-en-Y limb and the interposed jejunum is completed end-to-end by hand-sewing, followed by an end-to-side anastomosis between the proximal jejunum and the Roux-en-Y limb by hand-sewing, 40 cm from the other anastomosis (Fig. 1c, 2). This operation is indicated for a remnant gastric tumor that does not infiltrate the jejunogastrostomy, the interposed jejunum, or other adjacent organs such as the pancreas or duodenum. Patients with lymph node metastasis beyond the perigastric lymph nodes at stations #4d, 5 and 6 are not candidates for this surgery.

Results

We performed this operation on five patients: one woman and four men, with a median age of 60 years (range: 53–86; Table 1). Endoscopic mucosal resection was not indicated for any of these patients. The median operating time was 199 min (range: 175–259) and the estimated median blood loss was 330 ml (range: 300–730 ml). Although the adhesion between the remnant stomach and its adjacent organs could be dissected safely, resecting severe adhesions resulted in a longer operating time and more blood loss in some patients. None of the patients required intraoperative or postoperative blood transfusion.

A regular diet was resumed after a median period of 4 days (range: 4–5 days) and the median hospital stay was 13 days (range: 11–14 days) after surgery. There was no