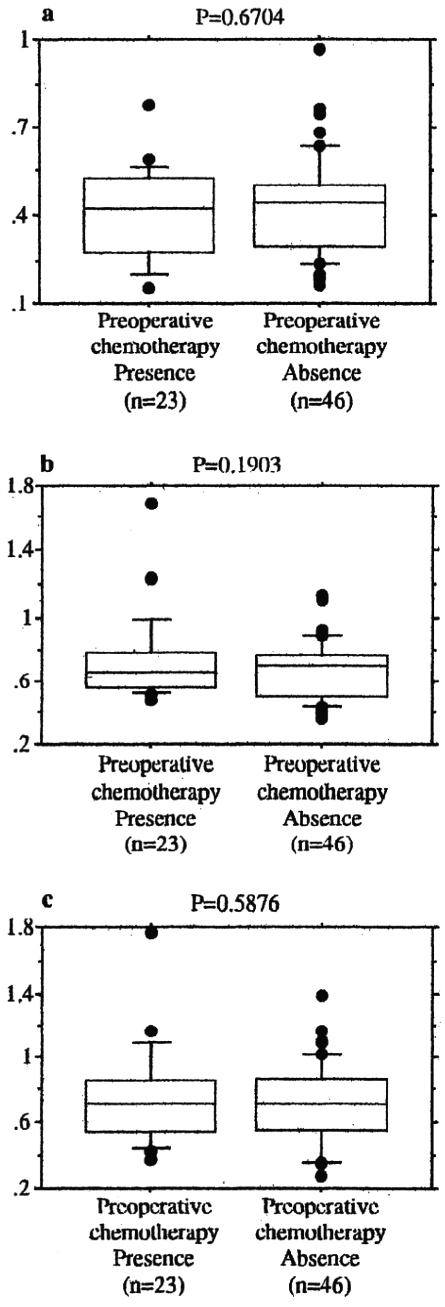

Fig. 4 Relationship between preoperative chemotherapy and E-PASS scores (**a** PRS, **b** SSS, and **c** CRS). Boxes show 95% confidence intervals

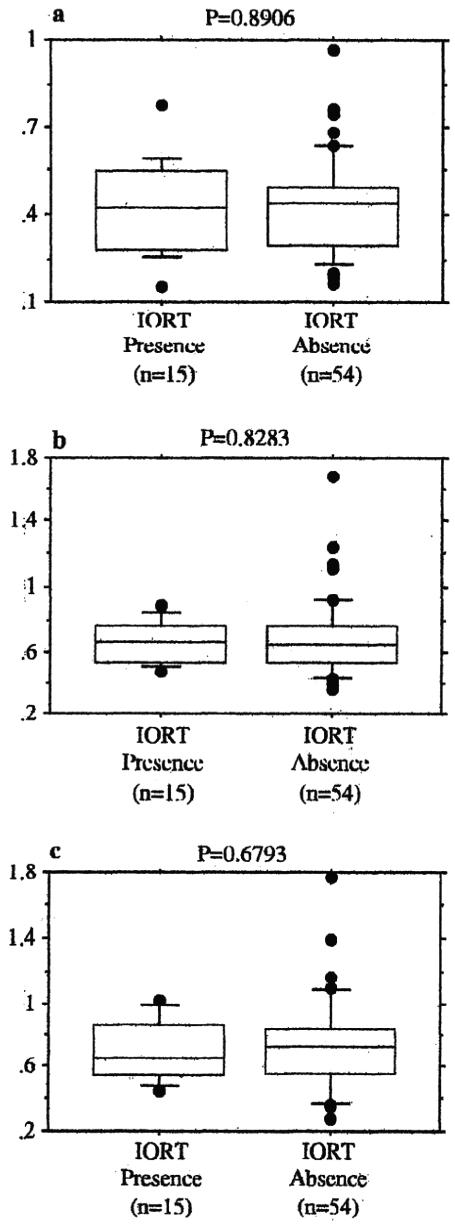

Fig. 5 Relationship between IORT and E-PASS scores (**a** PRS, **b** SSS, and **c** CRS). *Boxes* show 95% confidence intervals

esophagectomy for esophageal cancer [21]. In that study, the patients undergoing salvage esophagectomy with preoperative definitive chemoradiotherapy (CRT) had higher probability to have postoperative complications than those without preoperative CRT. Moreover, the SSS and CRS scores of patients with preoperative definitive CRT were significantly higher than those of patients without preoperative CRT. On the other hand, our present study indicated that there was no significant difference of morbidity rates and E-PASS scores between with and without preoperative chemotherapy and IORT. It indicated that preoperative chemotherapy and IORT could be adapted without significant extra risk for surgical complications.

In conclusion, E-PASS scoring system is a useful predictor associated with operative morbidity after elective PD. Neoadjuvant chemotherapy and IORT for periampullary carcinomas could be adapted without significant extra risk for surgical complication.

References

1. DeOliveira M, Winter J, Schafer M, Cunningham S, Cameron J, Yeo C, et al. Assessment of complications after pancreatic surgery a novel grading system applied to 633 patients undergoing pancreaticoduodenectomy. Ann Surg. 2006;244:931–9.
2. Khan A, Shah S, Agarwal A, Davidson B. Evaluation of the POSSUM scoring system for comparative audit in pancreatic surgery. Dig Surg. 2003;20:539–45.
3. Benzoni E, Saccomano E, Zompicchiatti A, Lorenzin D, Baccarani U, Adani G, et al. The role of pancreatic leakage on rising of postoperative complications following pancreatic surgery. J Surg Res. 2008;149:272–7.
4. Grobmyer S, Pieracci F, Allen P, Brennan M, Jaques D. Defining morbidity after pancreaticoduodenectomy: use of a prospective complication grading system. J Am Coll Surg. 2007;204:356–64.
5. Cheng Q, Zhang B, Zhang Y, Jiang X, Zhang B, Yi B, et al. Predictive factors for complications after pancreaticoduodenectomy. J Surg Res. 2007;139:22–9.
6. Topal B, Aerts R, Hendrickx T, Fieuws S, Penninckx F. Determinants of complications in pancreaticoduodenectomy. Eur J Surg Oncol. 2007;33:488–92.
7. House M, Fong Y, Arnaoutakis D, Sharma R, Winston C, Protic M, et al. Preoperative predictors for complications after pancreaticoduodenectomy: impact of BMI and body fat distribution. J Gastrointest Surg. 2008;12:270–8.
8. Shinchi H, Takao S, Maemura K, Aikou T. A new technique for pancreaticogastrostomy for the soft pancreas: the transfixing suture method. J Hepatobiliary Pancreat Surg. 2006;13:212–7.
9. Watanabe M, Usui S, Kajiwara H, Nakamura M, Sumiyama Y, Takada T, et al. Current pancreatogastrointestinal anastomotic methods: results of a Japanese survey of 3109 patients. J Hepatobiliary Pancreat Surg. 2004;11:25–33.
10. Yamaguchi K, Tanaka M, Chijiiwa K, Nagakawa T, Imamura M, Takada T. Early and late complications of pylorus-preserving pancreatoduodenectomy in Japan 1998. J Hepatobiliary Pancreat Surg. 1999;6:303–11.
11. Haga Y, Ikei S, Ogawa M. Estimation of physiologic ability and surgical stress (E-PASS) as a new prediction scoring system for postoperative morbidity and mortality following elective gastrointestinal surgery. Surg Today. 1999;29:219–25.
12. Oka Y, Nishijima J, Oku K, Azuma T, Inada K, Miyazaki S, et al. Usefulness of an estimation of physiologic ability and surgical stress (E-PASS) scoring system to predict the incidence of postoperative complications in gastrointestinal surgery. World J Surg. 2005;29:1029–33.
13. Japan Pancreas Society. General rules for the study of pancreatic cancer (5th edn). April 2002.
14. Japanese society of biliary surgery Society. General rules for surgical and pathological studies on cancer of the biliary tract (5th edn). September 2003.
15. Nishimura A, Sakata S, Iida K, Iwasaki Y, Takeshima T, Todoroki T, et al. Evaluation of intraoperative radiotherapy for carcinoma of the pancreas: prognostic factors and survival analyses. Radiat Med. 1988;6:85–91.
16. Nishimura A, Nakano M, Otsu H, Nakano K, Iida K, Sakata S, et al. Intraoperative radiotherapy for advanced carcinoma of the pancreas. Cancer. 1984;54:2375–84.
17. Takamori H, Hiraoka T, Kanemitsu K, Tsuji T, Tanaka H, Chikamoto A, et al. Long-term outcomes of extended radical resection combined with intraoperative radiation therapy for pancreatic cancer. J hepatobiliary Pancreat Surg. 2008;15:603–7.
18. Furue H. Criteria for the direct effect of chemotherapy against solid cancer by Japanese society for cancer therapy (in Japanese). J Jpn Soc Cancer Ther. 1986;21:931–42.
19. Haga Y, Wada Y, Takeuchi H, Kimura O, Furuya T, Sameshima H, et al. Estimation of physiologic ability and surgical stress (E-PASS) for a surgical audit in elective digestive surgery. Surgery. 2004;135:586–94.
20. http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_v30
21. Baba Y, Haga Y, Hiyoshi Y, Imamura Y, Nagai Y, Yoshida N, et al. Estimation of physiologic ability and surgical stress (E-PASS system) in patients with esophageal squamous cell carcinoma undergoing resection. Esophagus. 2008;5:81–6.
22. Winter J, Cameron J, Yeo C, Lillemoe K, Campbell K, Schulick R. Duodenojejunostomy leaks after pancreaticoduodenectomy. J Gastrointest Surg. 2008;12:263–9.
23. Hayashibe A, Kameyama M, Shinbo M, Makimoto S. The surgical procedure and clinical results of subtotal stomach preserving pancreaticoduodenectomy (SSPPD) in comparison with pylorus preserving pancreaticoduodenectomy (PPPD). J Surg Oncol. 2007;95:106–9.
24. Tang T, Walsh S, Fanshawe T, Seppi V, Sadat U, Hayes P, et al. Comparison of risk-scoring methods in predicting the immediate outcome after elective open abdominal aortic aneurysm surgery. Eur J Vasc Endovasc Surg. 2007;34:505–13.
25. Tang T, Walsh S, Fanshawe T, Gillard J, Sadat U, Varty K, et al. Estimation of physiologic ability and surgical stress (E-PASS) as a predictor of immediate outcome after elective abdominal aortic aneurysm surgery. Am J Surg. 2007;194:176–82.

Irinotecan Plus S–1 for Liver Metastases of Gastric Cancer

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ABSTRACT

Background/Aims: This retrospective study evaluated the efficacy of and compliance with combined irinotecan hydrochloride (CPT-11) and S-1 chemotherapy in patients with liver metastases of gastric cancer.

Methodology: A total of 28 gastric cancer patients with liver metastases received first-line chemotherapy. The response rate, overall survival, and toxicity were evaluated. Fourteen patients were treated with CPT-11+S-1 and they were compared with 14 patients who received *cis*-diamminedichloroplatinum (CDDP)+S-1.

Results: The CPT+S-1 group showed a higher response rate than the CDDP+S-1 group (57.1% [95%CI31.2-83.1%] vs. 42.9% [95%CI16.9-68.8%]; $p<0.44$). The median survival time of the CPT-11+S-1 group was significantly longer than the CDDP+S-1 group (16.1months [95%CI10.5-21.2] vs. 7.3months [95%CI2.2-14.7]; hazard ratio for death, 0.35 [95%CI 0.14-0.83]; $p<0.02$). By multivariate analysis for the treatment with CPT-11+S-1 was identified as an independent prognostic factor. The most common adverse effect of CPT-11+S-1 therapy was leukopenia (57.1%), which was Grade 3 in 3 patients (21.4%). However, all patients recovered rapidly and there were no significant differences of toxicity between the two regimens.

Conclusions: CPT-11+S-1 therapy will achieve significantly longer survival than CDDP+S-1 without severe toxicity in gastric cancer patients with liver metastases.

KEY WORDS: Cancer; Gastric; Metastasis; Liver; Chemotherapy; Prognosis; CPT–11 and S–1

ABBREVIATIONS: Topoisomerase I (Topo I); Median Survival Time (MST); Complete Response (CR); Partial Response (PR); Stable Disease (SD); Progressive Disease (PD)

INTRODUCTION

The prognosis of gastric cancer patients with liver metastases is poor, partly because multiple metastases are common. Palliative surgery cannot be expected to improve the survival of these patients (1-3). Their median survival time (MST) is reported to be 8.8 months (4), and a standard chemotherapy regimen has not yet been established.

Recently, several chemotherapy regimens that employ S-1, CDDP, and CPT-11 have achieved good response and survival outcomes in Japanese patients with gastric cancer, including those with unresectable tumors. S-1 is an oral anticancer drug that contains tegafur, a prodrug of 5-fluorouracil (5-FU), and the modulators 5-chloro-2,4-dihydroxypyridine (gimeracil) and potassium oxonate at a molar ratio of 1:0.4:1. The response rate to S-1 was 53.6% in an early phase II study and 44.6% in a late phase II study performed in patients with advanced gastric cancer, including previously treated patients (5-6). CPT-11 is an anticancer drug that inhibits the activity of topoisomerase I (Topo I) (7). It has achieved a response rate of 18.4% in eligible patients with advanced or recurrent gastric caner (8). Combined therapy with CPT-11 and S-1 has also been shown to be safe and effective, with response rates of 50% or better and an MST of 311-444 days. In particular, the combination of CPT-11 plus S-1 is reported to achieve a high response rate (58%) for liver metastases from gastric cancer when a certain regimen is employed (9-12).

This study was designed to assess the efficacy of treatment with CPT-11 plus S-1 for gastric cancer patients who had liver metastases by comparison with a control group who received CDDP plus S-1.

METHODOLOGY

Patients

Between January 2004 and December 2007, 14 gastric cancer patients with liver metastases were treated with CPT-11 plus S-1 as first-line chemotherapy. The response rate and overall survival of this group were compared with those of a historical control group, which was composed of 14 gastric cancer patients with liver metastases who received CDDP plus S-1 as first-line chemotherapy. The histological diagnosis was established by endoscopic biopsy in all patients. Staging was done by a complete physical examination, complete blood count and biochemical profile, gastrointestinal contrast study, total body computed tomography (CT) scanning, and abdominal ultrasound. Eligibility criteria were as follows: (1) measurable or assessable liver metastases; (2) age <80 years, (3) no prior chemotherapy, (4) no peritoneal metastasis, (5) performance status <3 (Eastern Cooperative Oncology Group scale), (6) ad-

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TABLE 1 Treatment Schedule

CPT-11+S-1	Weekly		
	1	2	3
TS-1 80mg/^{2} (po)	IIIIIII	IIIIIII	
CPT-11 90mg/^{2} (i.v. 2hr)	I	I	

CDDP+S-1	Weekly				
	1	2	3	4	5
TS-1 80mg/^{2} (po)	IIIIIII	IIIIIII		IIIIIII	
CDDP 70mg/^{2} (i.v. 2hr)	I				

TABLE 2 Baseline Characteristics

Clinical features	n (%) S-1+CPT-11 n=14	CDDP+S-1 n=14	*p* value
Gender			0.54
Male	12 (85.8)	13 (7.1)	
Female	2 (14.2)	1 (92.9)	
Age (Year)			
Median [Range]	66 [34-78]	67 [45-78]	
Gastrectomy			0.22
no	8 (57.1)	11 (78.6)	
yes	6 (42.9)	3 (21.4)	
Location			0.69
Upper	5 (35.7)	6 (42.9)	
Middle+Lower	9 (64.3)	8 (57.1)	
Liver metastasis			0.69
single metastasis	5 (35.7)	4 (28.6)	
multiple liver metastasis	9 (64.3)	10 (71.4)	
Lymph node metastasis			0.28
negative	3 (21.4)	1 (7.1)	
positive	11 (78.6)	13 (92.9)	
Histrogical type			0.62
Intestinal	12 (85.8)	11 (78.6)	
Diffuse	2 (14.2)	3 (21.4)	
CEA			0.22
negative	6 (42.9)	3 (21.4)	
positive	8 (57.1)	11 (78.6)	
CA19-9			0.13
negative	9 (64.3)	5 (35.7)	
positive	5 (35.7)	9 (64.3)	

equate hematologic, hepatic, renal and cardiac function (i.e., white blood cell count between 4,000 and 12,000/mm^3, absolute neutrophil count >2,000/mm^3, platelet count >100,000/mm^3, hemoglobin >9.5g/dl, transaminases within twice the upper limit of normal, serum bilirubin <1.5mg/dl, blood urea nitrogen <25mg/dl, and serum creatinine <1.5mg/dl), and (7) provision of written informed consent.

Treatment schedule

The CPT-11 plus S-1 regimen involved administration of CPT-11 (90mg/m^2) as a 2-h intravenous infusion on days 1 and 8, and administration of S-1 (80mg/m^2) once daily on days 1 to 14. This cycle was repeated every 3 weeks (**Table 1**). The regimen for the CDDP plus S-1 group was administration of S-1 (80 mg/m^2) once daily on days 1 to 14 and days 21 to 28, and administration of CDDP (70mg/m^2) as a 2-h intravenous infusion on day 8. This cycle was repeated every 5 weeks.

Evaluation

The response of measurable disease to treatment was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria (13). Tumor dimensions of liver metastasis were assessed by CT scanning. Adverse events that occurred during treatment were assessed according to the Common Toxicity Criteria of the National Cancer Institute (NCI-CTC) (National Cancer Institute 1999).

Statistical analysis

Overall survival curves were generated by the Kaplan-Meier method, and differences between the two groups were compared by the log-rank test. Prognostic factors were investigated by multivariate analysis with the Cox proportional hazards model. Statistical significance was accepted at a $p<0.05$.

RESULTS

Patients characteristics

The baseline characteristics of the patients in the CPT-11 plus S-1 group and the CDDP plus S-1 group are summarized in **Table 2**. There were no statistically significant differences between the two groups with regard to baseline characteristics.

Treatment and dose intensity

The mean number (mean ± SD) of CPT-11 plus S-1 treatment cycles was 11.5 ± 7.17 (range: 2-25), while the mean number of CDDP plus S-1 treatment cycles was 3.43 ± 2.21 (range: 1-7). After the failure of CPT-11 plus S-1 therapy, second-line chemotherapy was administered to 6 patients (docetaxel and/or CDDP).

Tumor response of liver metastasis

Among the 14 patients enrolled in the CPT-11 plus S-1 group, 2 patients achieved a complete response (CR), 6 achieved a partial response (PR), 4 showed no change (SD), and 2 had progressive disease (PD). The response rate was 57.1% (95% confidence interval (95%CI): 31.2-83.1%) (**Table 3**). In the CDDP plus S-1 group (n=14), 1 patient achieved CR, 5 achieved PR, 1 showed NC, and 8 had PD. The response rate was 42.9% (95%CI: 16.9-68.8%). There was a higher response rate with the CPT-11 plus S-1 regimen, but the difference was not significant ($p<0.44$).

Overall survival

The MST of the CPT-11 plus S-1 group was 16.1 months (95%CI: 10.5-21.2), while that of the CDDP plus S-1 group was 7.3 months (95%CI: 2.2-14.7) (**Figure 1**). Patients in the CPT-11 plus S-1 group showed significantly longer survival than those in the control group (hazard ratio for death, 0.35 (95%CI 0.14-0.83); $p<0.02$).

According to the results of multivariate analysis, treatment with CPT-11 plus S-1 was identified as an independent prognostic factor (**Table 4**).

Toxicity

All patients in the CPT plus S-1 received the complete regimen of chemotherapy as scheduled. As shown in **Table 5**, the most common adverse effects of CPT-11 plus S-1 were gastrointestinal toxicity (71.4%). Eight patients (57.1%) developed leukopenia of Grade 2 or more, and three patients (21.4%) had Grade 3 leukopenia. However, these patients recovered promptly after receiving granulocyte-colony stimulating factor (G-CSF). There were no significant differences of toxicity between the two regimens.

DISCUSSION

In this study, treatment with CPT plus S-1 achieved higher response rate and significantly better survival than CDDP plus S-1 without severe toxicity in gastric cancer patients who had liver metastases. Surgery may also provide better local control and prolong survival by tumor debulking in patients with advanced gastric cancer (14-15), but it is less effective in patients with very advanced disease and palliative surgery is unlikely to prolong the survival of such patients (16). In particular, the prognosis of gastric cancer patients with multiple liver metastases is still very poor (1-4).

Recently, several chemotherapy regimens have been developed based on the concept of biochemi-

TABLE 3 Tumor Response of Liver Metastasis

	n (%)				
CR	**PR**	**SD**	**PD**	**RR**	
CPT-11+S-1	2 (14.3)	6 (42.9)	4 (28.6)	2 (14.3)	8 (57.1)
CDDP+S-1	1 (7.1)	5 (35.7)	1 (7.1)	7 (50.0)	6 (42.9)

CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease; RR=response rate; CI=Confidence interval

TABLE 4 Multivariate Analysis

Clinical features	**Risk ratio**	**95%CI**	***p* value**
CA19-9			0.0003
negative	1		
positive	29.1	4.6-182.9	
Histrogical type			0.01
diffuse type	1		
intestinal type	12.5	1.8-85.6	
CPT-11+S-1			0.01
yes	1		
no	9.6	1.7-85.6	
CEA			0.01
negative	1		
positive	8.9	1.6-48.3	
Gastrectomy			0.19
no	1		
yes	4.2	0.5-36.9	
Lymph node metastasis			0.41
negative	1		
positive	4.2	0.1-140.9	
Gender			0.39
Female	1		
Male	6.7	0.1-495.2	
Age			0.67
>68	1		
≤68	1.4	0.3-6.4	
Location			0.71
Middle+Lower	1		
Upper	1.2	0.3-3.9	
Liver metastasis			0.97
single metastasis	1		
multiple liver metastasis	1.02	0.3-3.9	

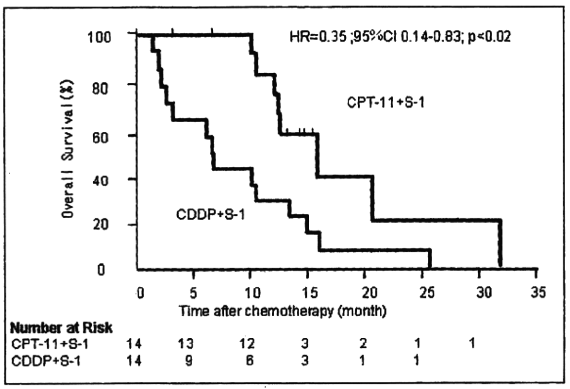

FIGURE 1 Survival of patients in the CPT-11+S-1 group and control group. Patients in the CPT-11+S-1 group had a significantly better survival than those with control group (p<0.02)

cal modulation, and have achieved a good clinical response in patients with gastric cancer. S-1 is a fluoropyrimidine that inhibits dihydropyrimidine dehydrogenase (DPD), and it has achieved the highest response rate among many oral anticancer agents in patients with unresectable advanced gastric cancer. Several phase I/II studies of combined therapy with CDDP plus S-1 that indicated a better efficacy have been performed in Japan and the USA (17-18). In these studies, the combination achieved a response rate of 74% and a median survival time of 383 days (18). The improved survival was suggested to be the result of a stronger effect on lymph node metastases (6, 17). Neoadjuvant chemotherapy with CDDP plus S-1 has also been examined in patients with metastatic disease involving more than 5 lymph nodes (19). It was reported that AFP-producing gastric cancer is characterized by frequent liver metastasis and can be treated successfully by preoperative combination chemotherapy (21-22). However, other studies have shown that a significant survival benefit is not achieved by chemotherapy in patients with liver metastases of gastric cancer (6, 17, 18). CPT-11 is an anticancer drug that inhibits topoisomerase I (Topo I) (7). Combined therapy with CPT-11 plus S-1 was developed in Japan and a higher response rate was reported (9-12). In phase I/II studies, this combination achieved a response rate of 62% and a median survival time of 444 days (11). Such results indicated that the efficacy of CPT-11 plus S-1 therapy was comparable to that of CDDP plus S-1. Especially in patients with renal dysfunction, CPT-11 plus S-1 could be recommended over CDDP plus S-1 therapy.

From 2002, we began using CDDP plus S-1 as first-line therapy for liver metastases of gastric cancer. However, the response rate was only 42.9%, which was lower than reported previously and the survival benefit achieved was not satisfactory. On the other hand, we noted a good response and better survival when CPT-11 plus S-1 was used as first-line treatment in patients with renal dysfunction. Therefore, we have applied this regimen as first-line treatment for liver metastases of gastric cancer since 2004. This study showed that the CPT-11 plus S-1 regimen caused fewer adverse events (21.4%) and achieved a better response rate (57.1%) in patients with liver metastases of gastric cancer, while also improving survival. In fact, the cumulative survival rate of the CPT-11 plus S-1 group was significantly better than that of the CDDP plus S-1 group (hazard ratio for death, 0.35 (95%CI 0.14-0.83); p<0.02). Prolongation of survival by this regimen may be explained by the chemosensitivity of liver metastases from gastric cancer to CPT-11. Treatment with CPT-11 plus S-1 was identified as an independent prognostic factor by multivariate analysis, suggesting that treating liver metastases may improve the prognosis of gastric cancer patients. To our knowledge, this is the first report in which survival was compared between CPT-11 plus S-1 and CDDP plus S-1 regimens.

The present study conclude that CPT-11 plus S-1 therapy is effective against advanced gastric cancer and improves the prognosis. Curative surgery may also become possible after CPT-11 plus S-1 therapy, resulting in long-term disease-free survival. Moreover, this regimen could be improved further by adding other new anticancer drugs such as docetaxel, oxaliplatin, or molecular-targeting agents.

TABLE 5 Adverse Events of Chemotherapy

n(%)

	CPT-11+TS-1		CDDP+TS-1	
	All grades	Grade3	All grades	Grade3
Leukopenia	8 (57.1)	3 (21.4)	8 (57.1)	1 (7.1)
Noutropenia	8 (57.1)	3 (21.4)	4 (28.6)	1 (7.1)
Thrombocytopenia	0 (0)	0 (0)	4 (28.6)	3 (21.4)
Nausea/Vomit	10 (71.4)	1 (7.1)	9 (64.8)	0 (0)
Diarrhea	4 (28.6)	1 (7.1)	4 (28.6)	0 (0)
Hand-foot skin reaction	4 (28.6)	0 (0)	4 (28.6)	0 (0)
Alopecia	6 (42.9)	0 (0)	2 (14.3)	0 (0)
Liver dysfunction	1 (7.1)	0 (0)	1 (7.1)	0 (0)

REFERENCES

1. **Sakamoto J, Nakazato H, Teramukai S, Ohashi Y, Takahashi Y, Mai M, Toge T, Okura H, Kodaira S, Maetani S, Okajima K, Nomoto K, Hattori T, Inokuchi K:** Association between preoperative plasma CEA levels and the prognosis of gastric cancer following curative resection. Tumor Marker Committee, Japanese Foundation for Multidisciplinary Treatment of Cancer, Tokyo, Japan. Surg Oncol 1996; 5:133-139
2. **Roh HR, Suh KS, Lee HJ, Yang HK, Choe KJ, Lee KU:** Outcome of hepatic resection for metastatic gastric cancer. Am Surg 2005;71:95-99.
3. **Ohkuwa M, Ohtsu A, Boku N, Yoshida S, Miyata Y, Shirao K, Shimada Y, Kurihara M:** Long-term results for patients with unresectable gastric cancer who received chemotherapy in the Japan Clinical Oncology Group (JCOG) trials. Gastric cancer 2000;3:145-150.
4. **Zacherl J, Zacherl M, Scheuba C, Steininger R, Wenzl E, Mühlbacher F, Jakesz R, Längle F:** Analysis of hepatic resection of metastasis originating from gastric adenocarcinoma. J Gastrointest Surg 2002;6:682-689.
5. **Sugimachi K, Maehara Y, Horikoshi N, Shimada Y, Sakata Y, Mitachi Y, Taguchi T:** An early phase study of oral S-1, a newly developed 5-fluorouracil derivative for advanced and recurrent gastrointestinal cancers: The S-1 Gastrointestinal Cancer Study Group. Oncology 1999;57:202-210
6. **Sakata Y, Ohtsu A, Horikoshi N, Sugimachi K, Mitachi Y, Taguchi T:** Late phase II study of novel oral fluoropyrimidine anticancer drug S-1 (1 M tegafur-0.4 M gimestat-1 M otastat potassium) in advanced gastric cancer patients. Eur J Cancer 1998; 34:1715-1720.
7. **Kawano Y, Aonuma M, Hirota Y, Kuga H, Sato K:** Intracellular roles of SN-38, a metabolite of the camptothecin derivative CPT-11, in the antitumor effect of CPT-11. Cancer Res 1991;51:4187-4191
8. **Research group of CPT-11 in Gynecologic Cancers:** An early phase II trial of CPT-11 in patients with advanced gastrointestinal cancer. J Jpn Soc Cancer Ther 1992;27:2028-2035
9. **Takiuchi H, Narahara H, Tsujinaka T, Gotoh M, Kawabe S, Katsu K, Iishi H, Tatsuta M, Fujitani K, Furukawa H, Taguchi T:** Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG): Phase I study of S-1 combined with irinotecan (CPT-11) in patients with advanced gastric cancer (OGSG 0002). Jpn J Clin Oncol. 2005;35:520-525.
10. **Yamada Y, Yasui H, Goto A, Arai T, Ura T, Hamaguchi T, Muro K, Shimada Y, Shirao K:** Phase I study of irinotecan and S-1 combination therapy in patients with metastatic gastric cancer. Int J Clin Oncol 2003;8:374-380
11. **Inokuchi M, Yamashita T, Yamada H, Kojima K, Ichikawa W, Nihei Z, Kawano T, Sugihara K:** Phase I/II study of S-1 combined with irinotecan for metastatic advanced gastric cancer. Br J Cancer 2006;94:1130-1135
12. **Katsube T, Ogawa K, Ichikawa W, Fujii M, Tokunaga A, Takagi Y, Kocji M, Hayashi K, Kubota T, Aiba K, Arai K, Terashima M, Kitajima M:** Phase I/II study of irinotecan (CPT-11) and S-1 in the treatment of advanced gastric cancer. Anti-cancer Drugs 2007;18:605-610
13. **Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG:** New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer inst 2000;92:205-216.
14. **Degiuli M, Sasako M, Ponti A, Calvo F:** Survival results of a multicentre phase II study to evaluate D2 gastrectomy for gastric cancer. Br J Cancer. 2004; 4:1727-32.
15. **Edwards P, Blackshaw GR, Lewis WG, Barry JD, Allison MC, Jones DR:** Prospective comparison of D1 vs modified D2 gastrectomy for carcinoma. Br J Cancer.2004;17:1888-1892.
16. **Bonenkamp JJ, Hermans J, Sasako M, van de Velde CJ, Welvaart K, Songun I, Meyer S, Plukker JT, Van Elk P, Obertop H, Gouma DJ, van Lanschot JJ, Taat CW, de Graaf PW, von Meyenfeldt MF, Tilanus H:** Dutch Gastric Cancer Group: Extended lymph-node dissection for gastric cancer. N Engl J Med 1999;25:908-914.
17. **Ajani JA, Faust J, Ikeda K, Yao JC, Anbe H, Carr KL, Houghton M, Urrea P:** Phase I pharmacokinetic study of S-1 plus cisplatin in patients with advanced gastric carcinoma. J Clin Oncol 2005;1:6957-6965.
18. **Koizumi W, Tanabe S, Saigenji K, Ohtsu A, Boku N, Nagashima F, Shirao K, Matsumura Y, Gotoh M:** Phase I/II study of S-1 combined with cisplatin in patients with advanced gastric cancer. Br J Cancer 2003;15:2207-2212.
19. **Kochi M, Fujii M, Kanamori N, Kaiga T, Takahashi T, Kobayashi M, Takayama T:** Neoadjuvant chemotherapy with S-1 and CDDP in advanced gastric cancer. Cancer Res Clin Oncol. 2006 ;132:781-785.
20. **Nakajima T, Nashimoto A, Kitamura M, Kito T, Iwanaga T, Okabayashi K, Goto M:** Adjuvant mitomycin and fluorouracil followed by oral uracil plus tegafur in serosa-negative gastric cancer: a randomised trial. Gastric Cancer Surgical Study Group. Lancet 1999;24:273-277.
21. **Kochi M, Fujii M, Kaiga T Takahashi T, Morishita Y, Kobayashi M, Kasakura Y, Takayama T:** FLEP chemotherapy for alpha-fetoprotein-producing gastric cancer. Oncology 2004;66:445-449
22. **Ihling C, Schaefer HE, Baumgartner U, Riede UN:** Hepatoid adenocarcinoma of the stomach: a case report. Gen Diagn Pathol 1995;141:61-65.

Transplant International

LETTER TO THE EDITOR

Use of a bridging autologous hepatic vein graft for extended right-liver transplantation

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Living-donor liver transplantation (LDLT) using a right-liver graft is a routine procedure in adults. The use of an allogenic cryopreserved vein for hepatic vein reconstruction facilitates full vascularization and minimizes graft congestion [1]. However, there is a constant risk of graft shortage in such procedures. In this study, we have reported the use of an autologous hepatic vein extracted from the resected liver of the recipient for overcoming graft shortage during hepatic vein reconstruction.

A 53-year-old man with hepatitis B cirrhosis underwent LDLT; the donor was his 31-year-old son. The graft weighed 740 g, and it included a right hepatic vein (RHV), middle hepatic vein (MHV), middle RHV (mRHV), and inferior RHV (iRHV). We decided to use a cryopreserved iliac vein (length, 65 mm; diameter, 22 mm) as a homograft for reconstructing the hepatic veins. The double inferior vena cava (IVC) method was used to obtain a sufficient length of the cryopreserved vein for anastomosis to the RHV and iRHV [1]. The other short hepatic veins, including the MHV, were to be anastomosed directly to the homograft.

Hepatic vein reconstruction using the homograft was performed on the back table (Fig. 1). The superior end of the homograft was sealed with continuous sutures. End-to-end anastomoses were performed between the inferior forked ends of the homograft and the iRHV and mRHV and between the RHV and the homograft. However, the venous graft was insufficient for direct anastomosis of the MHV to the homograft. Therefore, we used the RHV from the diseased liver as an autologous bridging vein graft.

The recipient's IVC was semi-clamped, and a 5-cm-long longitudinal incision was made. The homograft was incised similarly and anastomosed to the IVC in a side-to-side manner. Computed tomography after transplantation revealed clear enhancement of the hepatic veins, the homograft and the autologous graft. There was no stenosis of the anastomosis (Fig. 2). The patient is doing well 40 months after transplantation.

Living-donor liver transplantation (LDLT) with an extended right-liver graft requires hepatic vein reconstruction with multiple anastomoses, and various procedures

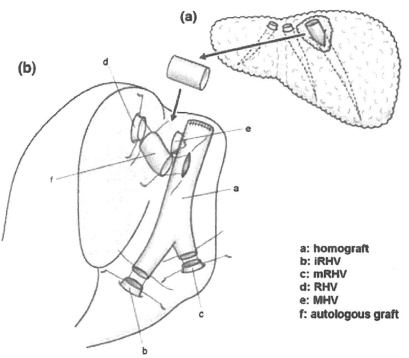

Figure 1 Hepatic venous reconstruction. (a) The RHV was extracted from the resected liver. (b) The anastomosis of the RHV, MHV, iRHV and mRHV to the homograft and the autologous hepatic vein graft was performed on the back table.

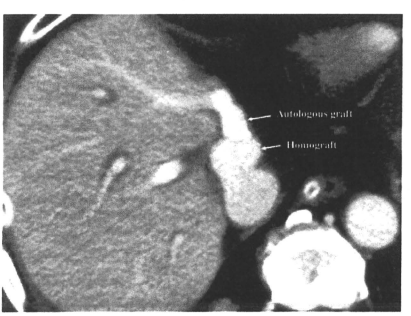

Figure 2 A computed tomographic scan obtained 1 week after transplantation. The autologous graft and homograft are clearly enhanced, suggesting good drainage and patency.

have been described for venous reconstruction [2–4]. Graft congestion can be minimized by reconstructing the short hepatic veins, such as the mRHV and iRHV, along with the MHV and RHV [3]. In our case, the distance between the MHV and homograft was longer than what we had anticipated; therefore, we faced a shortage of the cryopreserved venous graft. In this situation, we considered two options for venous reconstruction: one was a separate, direct anastomosis of the MHV, and the other was the extraction of an autologous venous graft from a hepatic vein of the resected liver or from the recipient's saphenous vein. Procurement of a venous graft from the resected liver is a less invasive and more convenient procedure. However, extraction of an autologous graft from the saphenous vein is recommended if the resected liver is carcinomatous. We have successfully used a similar bridging autologous graft for portal vein reconstruction [5].

Thus, a bridging autologous hepatic vein graft extracted from the resected liver is a convenient alternative graft for hepatic venous reconstruction in LDLT.

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References

1. Sugawara Y, Makuuchi M, Akamatsu N, *et al.* Refinement of venous reconstruction using cryopreserved veins in right liver grafts. *Liver Transpl* 2004; **10**: 541.
2. Lo CM, Fan ST, Liu CL, *et al.* Extending the limit on the size of adult recipient in living donor liver transplantation using extended right lobe graft. *Transplantation* 1997; **63**: 1524.
3. Liu CL, Zhao Y, Lo CM, Fan ST. Hepatic venoplasty in right lobe live donor liver transplantation. *Liver Transpl* 2003; **9**: 1265.
4. Kasahara M, Takada Y, Fujimoto Y, *et al.* Impact of right lobe with middle hepatic vein graft in living-donor liver transplantation. *Am J Transplant* 2005; **5**: 1339.
5. Yamazaki S, Takayama T, Inoue K, Higaki T, Makuuchi M. Interposition of autologous portal vein graft in left liver transplantation. *Liver Transpl* 2005; **11**: 1615.

RECONSTRUCTION BY LATERAL PANCREATICOGASTROSTOMY AFTER PANCREATODUODENECTOMY

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Original Article

RECONSTRUCTION BY LATERAL PANCREATICOGASTROSTOMY AFTER PANCREATODUODENECTOMY

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Radical resection by pancreatoduodenectomy and decompression of the sclerotic pancreatic duct is a requisite treatment for patients with cancer of the head of the pancreas complicated by chronic pancreatitis. This report describes a novel technique involving side-to-side pancreaticogastrostomy following pancreatoduodenectomy to effect decompression of the pancreatic duct in such patients. The procedure involves the initial opening of the pancreatic duct by means of a longitudinal incision, followed by incision of the posterior gastric wall and side-to-side anastomosis of the pancreas with it. The technique offers a safe method of reconstruction after radical resection of pancreatic cancer and, as a surgical therapy for chronic pancreatitis, can effectively improve patient quality of life.

Introduction

For patients with chronic pancreatitis accompanied by intrapancreatic ductal stone, protein plaque, and chronic pain, the most common drainage procedure involving lateral pancreaticojejunostomy is known to be effective.[1,2] Furthermore, cancer of the head of the pancreas may occasionally develop in patients with chronic pancreatitis,[3] and pancreatoduodenectomy (the Whipple procedure) is indicated. This report describes a novel technique that employs lateral pancreaticogastrostomy to bring about an effective decompression of the pancreatic duct after pancreatoduodenectomy in patients with cancer of the head of the pancreas complicated by chronic pancreatitis.

Surgical Technique

Our procedure is indicated for patients with cancer of the head of the pancreas, together with a dilated main pancreatic duct due to chronic pancreatitis, and/or intraductal calculi. Radical resection of the cancer by pancreatoduodenectomy and

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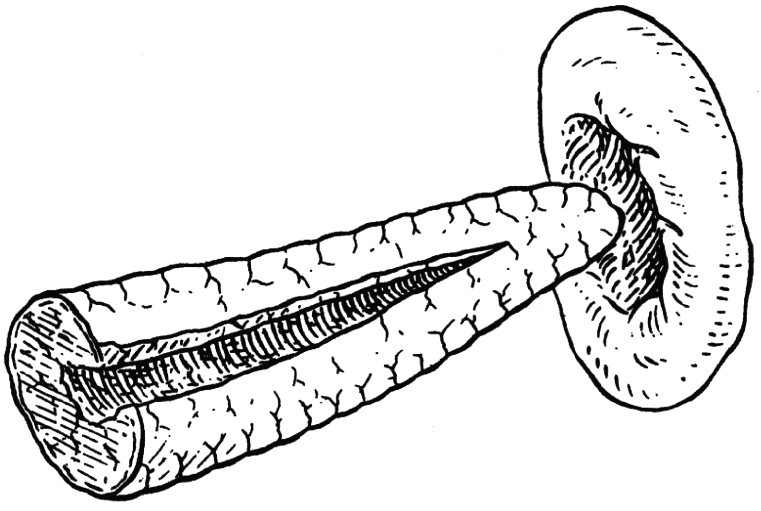

Fig. 1. The main pancreatic duct is opened longitudinally. Pancreatic stones and plaques are removed.

decompression for chronic pancreatitis are scheduled. If no lymph node metastases are observed around the pylorus, pylorus-preserving pancreatoduodenectomy is carried out. Under guidance, with a probe inserted into the main pancreatic duct through the pancreatic stump, the anterior wall of the pancreas is incised longitudinally and the main pancreatic duct is opened (Fig. 1). During this procedure, all pancreatic stones and plaques are removed. After determining a suitable position, the posterior gastric wall is incised longitudinally. It is better to make the incision in the posterior gastric wall slightly shorter than the length of the opened main pancreatic duct. The anterior gastric wall is also incised to allow direct visual observation of the area to be sutured. The pancreatic stump is anastomosed to the posterior wall of the gastric body in two layers: duct-to-mucosa with absorbable 4-0 interrupted sutures, and pancreatic parenchyma-to-gastric seromuscular layer with 3-0 interrupted sutures (Fig. 2). The patency of the lumen is confirmed through the window opened in the anterior gastric wall, and a check is made to ensure that the sutures are watertight (Fig. 3). An end-to-end anastomosis instrument is inserted through the gastric window, and gastrojejunostomy is performed (Fig. 4). Cholangiojejunostomy is performed 10 cm distal to the gastrojejunal anastomosis. In addition to introducing an indwelling nasogastric tube in the region of the pancreaticogastric anastomosis, gastrostomy is performed (Fig. 5). No pancreatic leakage has so far occurred in any of the 5 patients on whom we

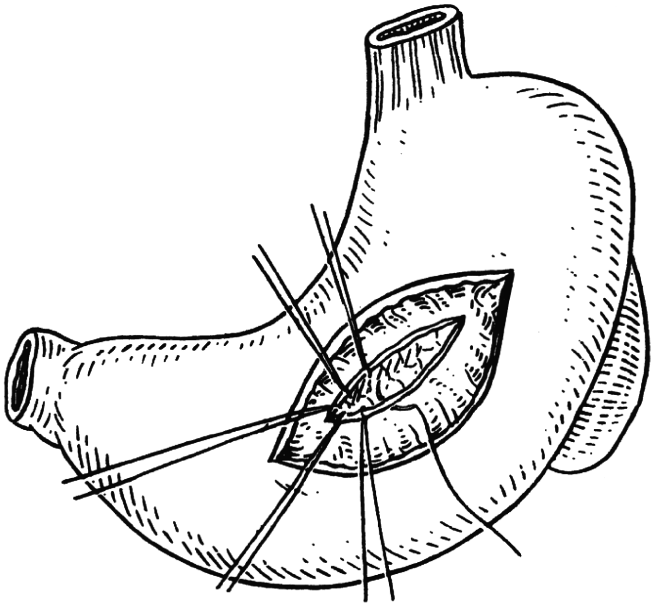

Fig. 2. The pancreatic stump is anastomosed to the posterior wall of the gastric body in two layers.

have performed this procedure. The drainage from the gastrostomy has been 1500 to 2000 ml per day for the first postoperative week. Oral ingestion has been initiated at 2 or 3 weeks after surgery. Two patients who were alive at 5 years after surgery, having experienced no recurrence of their cancer, were free of symptoms of pancreatitis, and their secretion of pancreatic juice was confirmed by gastroendoscopy. In all 5 patients, the serum amylase levels and N-benzoyl-L-tyrosyl-*p*-aminobenzoic acid test results were within the normal ranges. Their body weights were increased at 1 year after surgery, and their oral dietary intake was adequate. No aggravation of diabetes was observed in any patient.

Discussion

The main features of the technique of side-to-side pancreaticogastrostomy described here are: 1) prevention of pancreatic leakage, 2) drainage of the pancreatic juice, 3) decompression of the stomach by gastrostomy, and 4) the simple nature of the technique using an end-to-end anastomosis instrument and preservation of physiological digestion and absorption by Billroth I-like reconstruction. The prevention of pancreatic leakage, the continuance of physiological digestion and absorption, and the

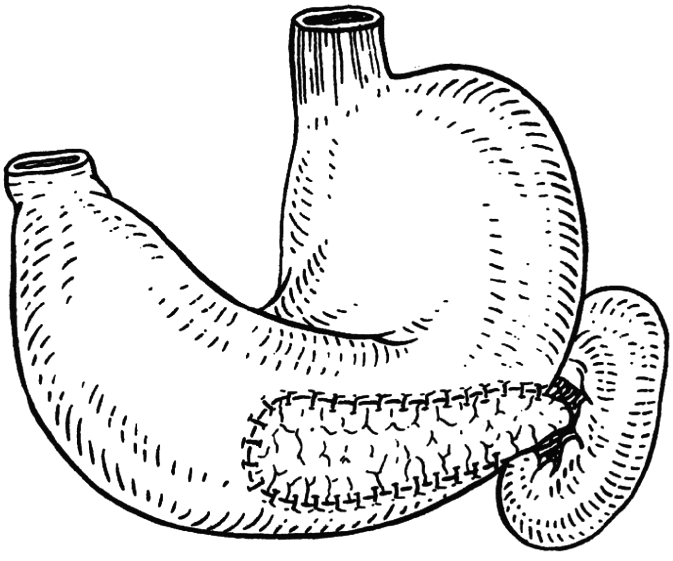

Fig. 3. The pancreatic stump and incised region of the posterior gastric wall are sutured in a side-to-side manner.

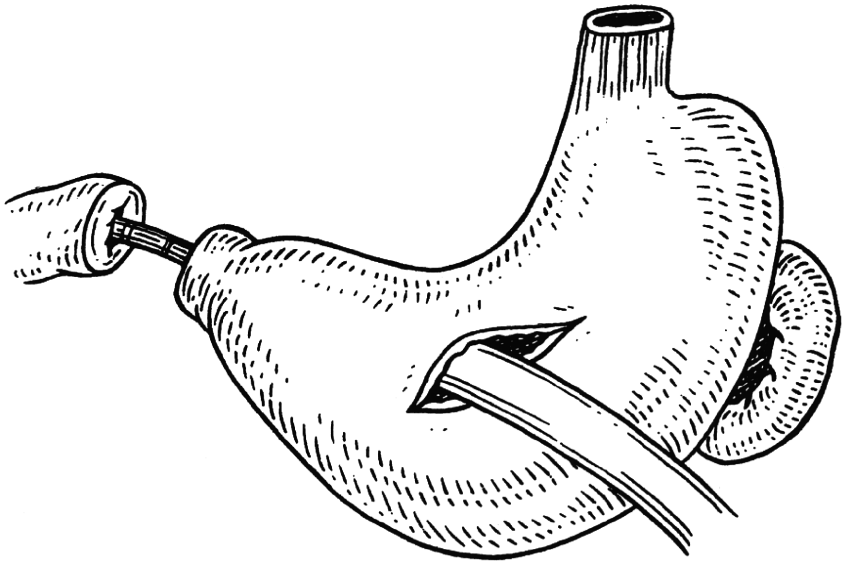

Fig. 4. Gastrojejunostomy is performed with an end-to-end anastomosis.

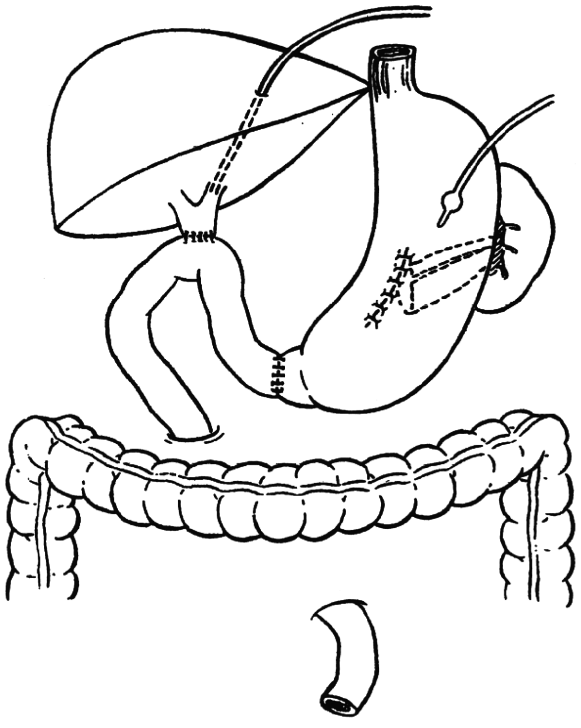

Fig. 5. Cholangiojejunostomy and gastrostomy are performed.

preservation of residual pancreatic endocrine function are necessary features of reconstructive methods performed after pancreatoduodenectomy.[4,5] Pancreaticogastrostomy is technically easy to carry out and is widely accepted as a means of preventing pancreatic leakage.[6] Since the blood supply in the gastric wall is greater than that in the jejunum, the gastric wall is appropriate for anastomosis with the pancreas. We adopted duct-to-mucosa anastomosis because this procedure may be safer in pancreaticogastrostomy as reported in pancreaticojejunostomy.[7] In addition, the anastomosis site can be seen directly by opening the anterior gastric wall, which allows reliable suturing. Although pancreatic juice enters the stomach directly, and changes the gastric pH, good digestion and absorption have been reported.[8] However, delayed initiation of oral ingestion as a consequence of gastric stasis is an occasional problem.

The present procedure is well indicated for patients with curable cancer of the head of the pancreas, together with a dilated main pancreatic duct due to severe chronic pancreatitis, and/or obstructive intraductal calculi. Full-length incision of the

main pancreatic duct and complete removal of calculi and plaque are required for rescue in cases of severe pancreatitis with chronic symptoms. Our reconstructive procedure provides adequate decompression by means of side-to-side anastomosis along the full length of the main pancreatic duct, and offers a novel means of improving the prognosis of patients with pancreatic cancer as well as their quality of life as affected by chronic pancreatitis.

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References

1) Puestow, C.B., Gillesby, W.J.: Retrograde surgical drainage of pancreas for chronic relapsing pancreatitis. *Arch Surg* **76** 898–907 (1958)
2) Partington, P.F., Rochelle, R.E.: Modified Puestow procedure for retrograde drainage of the pancreatic duct. *Ann Surg* **152** 1037–1043 (1960)
3) Bansal, P., Sonnenberg, A.: Pancreatitis is a risk factor for pancreatic cancer. *Gastroenterology* **109** 247–251 (1995)
4) Fujino, Y., Suzuki, Y., Ajiki, T., Tanioka, Y., Ku, Y., Kuroda, Y.: Risk factors influencing pancreatic leakage and the mortality after pancreaticoduodenectomy in a medium-volume hospital. *Hepatogastroenterology* **49** 1124–1129 (2002)
5) Z'graggen, K., Uhl, W., Friess, H., Buchler, M.W.: How to do a safe pancreatic anastomosis. *J Hepatobil Pancreat Surg* **9** 733–737 (2002)
6) Oussoultzoglou, E., Bachellier, P., Bigourdan, J.M., Weber, J.C., Nakano, H., Jaeck, D.: Pancreaticogastrostomy decreased relaparotomy caused by pancreatic fistula after pancreaticoduodenectomy compared with pancreaticojejunostomy. *Arch Surg* **139** 327–335 (2004)
7) Poon, R.T., Lo, S.H., Fong, D., Fan, S.T., Wong, J.: Prevention of pancreatic anastomotic leakage after pancreaticoduodenectomy. *Am J Surg* **183** 42–52 (2002)
8) Shyr, Y.M., Su, C.H., Wu, C.W., Lui, W.Y.: Gastric pH and amylase and safety for non-stented pancreaticogastrostomy. *Hepatogastroenterology* **49** 1747–1750 (2002)

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How Do We Predict the Clinically Relevant Pancreatic Fistula After Pancreaticoduodenectomy?—An Analysis in 244 Consecutive Patients

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Abstract

Background The most important problem in pancreatic fistula is whether one can distinguish clinical pancreatic fistula, grade B + C fistula by the International Study Group on Pancreatic Fistula (ISGPF), from transient pancreatic fistula (grade A), in the early period after pancreaticoduodenectomy (PD). It remains unclear what predictive risk factors can precisely predict which clinical relevant or transient pancreatic fistula when diagnosed pancreatic fistula on POD3 by ISGPF criteria.

Methods We analyzed the predictive factors of clinical pancreatic fistula by logistic regression analysis in 244 consecutive patients who underwent PD. Pancreatic fistula was classified into three categories by ISGPF.

Results The rate of pancreatic fistula was 69 of 244 consecutive patients (28%) who underwent PD. Of these, 47 (19%) had grade A by ISGPF criteria, 17 patients (7.0%) had grade B, and five patients (2.0%) had grade C. The independent risk factor of incidence of pancreatic fistula is soft pancreatic parenchyma. However, soft pancreatic parenchyma did not predict underlying clinically relevant pancreatic fistula. The independent predictive factors of clinically relevant pancreatic fistula were serum albumin level $\leq$3.0 g/dl on postoperative day (POD) 4 and leukocyte counts >9,800 mm^{-3} on POD 4. Positive predictive value of the combination of two predictive factors for clinical relevant pancreatic fistula was 88%.

Conclusions The combination of two factors on POD4, serum albumin level $\leq$3.0 g/dl and leukocyte counts >9,800 mm^{-3}, is predictive of clinical relevant pancreatic fistula when diagnosed pancreatic fistula on POD 3 by ISGPF criteria.

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Introduction

The morbidity rate after pancreaticoduodenectomy (PD) remains high (30–65%), although, with recent advances in surgical techniques and perioperative management, the mortality rate has decreased to less than 5% [1–4]. In particular, pancreatic fistula, with an incidence varying between 5 and 20% in most series, has been reported to be associated with a higher incidence of such life-threatening complications as intra-abdominal abscess, intra-abdominal bleeding, and sepsis [5–8]. In 2005, an international study group of pancreatic surgeons (ISGPF) proposed a consensus definition and clinical grading about postoperative pancreatic fistula [9]. The most important problem in pancreatic fistula is whether one can distinguish clinically relevant pancreatic fistula, grade B + C fistula by ISGPF, from transient pancreatic fistula, grade A, in the early period after PD. Various previous reports have evaluated the perioperative factors that influence the incidence of pancreatic fistula, such as soft pancreatic parenchyma, small main pancreatic duct, and intraoperative bleeding [10–14]. However, these risk factors of incidence of pancreatic fistula could not always predict the extent of severe clinical pancreatic fistula. Thus it remains unclear what predictive risk factors can precisely distinguish clinically relevant pancreatic fistula from transient pancreatic fistula in the early postoperative period. The goal of the present study was to predict whether clinically relevant or transient

pancreatic fistula can influence patient management when diagnosed on POD 3 by ISGPF criteria. We evaluated the factors leading to clinically relevant pancreatic fistula in the early period after PD.

Methods

Patients

From February 2003 to December 2008, 244 consecutive patients underwent PD and were analyzed in terms of various factors at Wakayama Medical University Hospital (WMUH). Preoperative biliary drainage was performed by percutaneous transhepatic catheter drainage or endoscopic nasal biliary drainage, when the serum levels of total bilirubin were greater than 3 mg/dl or when dilatation of the intrahepatic bile duct and hepatic dysfunction (transaminase: more than 100 IU/ml) were detected. Patient characteristics and perioperative and postoperative parameters were reviewed for the following clinical variables: patient age, gender, preoperative serum level of albumin (normal range: 3.8–5.1 g/dl), total bilirubin (normal range: 0.2–1.2 mg/dl) and amylase (normal range: 0.2–1.2 mg/dl), history of jaundice, history of diabetes mellitus, preoperative biliary drainage, type of resection (PD or pylorus-preserving pancreaticoduodenectomy [PpPD]), operative time, intraoperative bleeding, red blood cell transfusion, pancreatic texture (soft or hard), presence or absence of dilatation of the main pancreatic duct, histologic diagnosis (malignant or benign), and serum amylase level and amylase level of drainage fluid on POD 1, 3, and 4.

Perioperative Management

All patients underwent PD with Child reconstruction and PpPD with Traverso reconstruction. Pancreatic anastomosis after PD and PpPD was performed by duct-to-mucosa, end-to-side pancreaticojejunostomy in all patients. External suture rows were performed as a single suture between the remnant pancreatic capsule, parenchyma, and jejunal seromuscular area by means of an interrupted suture line of 4-0 Novafil (polybutester, Tyco Healthcare Japan Co., Tokyo). Internal suture rows, duct to mucosa, were created between the pancreatic ductal and jejunal mucosa with 8 interrupted 5-0 PDS-II (polydioxanone, Johnson and Johnson Co., Tokyo). A 5-French polyethylene pancreatic duct drainage tube (Sumitomo Bakelite Co., Tokyo, Japan) was used as a stent for pancreaticojejunostomy in all patients. No stent was used for the biliary anastomosis. One 10-mm Penrose drain (a silicon, multitubular flat drain) was routinely placed anterior to the pancreaticojejunostomy. This drain was connected to a closed drainage system. The drains were to be removed on POD 4 in all enrolled patients if bile leakage and bacterial contamination were absent [1]. Dilatation of the pancreatic duct was defined as a diameter greater than 3 mm and was judged by the measurement of preoperative computed tomographic (CT) imaging and, again, intraoperatively. The amylase of serum and drainage fluid was measured on POD 1, 3, and 4.

No patient received radiotherapy preoperatively or postoperatively. All patients received prophylactic antibiotics intraoperatively and for 2 days postoperatively. Prophylactic octreotide was not postoperatively administered to prevent pancreatic fistula.

Postoperative Complications

Pancreatic fistula was determined by the guideline of the International Study Group on Pancreatic Fistula (ISGPF) [9]: amylase level in drainage fluid on POD 3 more than 3 times the serum amylase level. Pancreatic fistula is classified into three categories by ISGPF as follows: grade A: "transient pancreatic fistula" (no clinical impact); grade B: requires a change in management or adjustment in the clinical pathway; grade C: requires a major change in clinical management or deviation from the normal clinical pathway. Combined grade B + C is defined as "clinical pancreatic fistula."

Biliary fistula was defined as the presence of bile in the drainage fluid that persisted to POD 4. Intra-abdominal abscess was defined as intra-abdominal fluid collection with positive cultures identified by ultrasonography (US) or computed tomography associated with persistent fever and elevated white blood cells. Infected intra-abdominal fluid was defined as drainage fluid having a positive culture with clinical signs, but without an intra-abdominal abscess being detected. Delayed gastric emptying was defined as output from a nasogastric tube of greater than 500 ml per day that persisted beyond POD 10, the failure to maintain oral intake by POD 14, or reinsertion of a nasogastric tube. Increased leukocyte counts on POD 4 was defined as elevated leukocyte counts compared to POD 1 with greater than the normal upper limit (9,800 mm^{-3}). All patients in this study were followed by physical examination, laboratory data, and radiological technique such as US or CT scan for 3 months after pancreaticoduodenectomy to detect complications.

Statistical Analysis

Data were expressed as means ± SD. Patient characteristics and perioperative and postoperative factors between the two groups were compared by chi-square statistics, Fisher's exact test, and the Mann–Whitney *U*-test. Variables with $P < 0.100$ were entered into a logistic

regression model to determine independent risk factors of postoperative complications. The independent risk factors of the variables were expressed as odds ratios with their 95% confidence intervals. The optimal cut-off levels of serum albumin level on POD 4 for differentiation between the group with intra-abdominal abscess and the group without intra-abdominal abscess were sought by constructing receiver operating characteristics (ROC) curves, which were generated by calculating the sensitivities and specificities of serum albumin level on POD 4 at several predetermined cut-off points. Line graphs were used for graphic visualization (SPSS Inc., Chicago, IL). Statistical significance was defined as $P < 0.05$.

Results

Characteristics of Patients and Perioperative Status

A total of 244 consecutive patients (137 men and 107 women) underwent PD. The mean age of patients was 68 ± 10 years (range: 35–87 years), and the indications for PD in the 244 patients were as follows: 76 pancreatic adenocarcinoma, 46 bile duct carcinoma, 23 ampullary adenocarcinoma, 29 intraductal papillary adenoma, 30 intraductal papillary carcinoma, 6 duodenal adenocarcinoma, 6 pancreatic endocrine tumor, 1 solid pseudopapillary tumor, 13 chronic pancreatitis, 3 serous cyst adenoma, 2 metastatic pancreatic carcinoma, and 9 other disease. Of these, 190 patients (78%) had malignancy and 54 (22%) had benign disease.

Of the 244 patients, 39 patients underwent PD with Child reconstruction and 205 patients underwent PpPD with Traverso reconstruction. Combined portal vein resection was performed in 25 patients (10.2%). Mean operative time was 363 ± 72 min (range: 185–609 min), mean operative bleeding was 1,054 ± 1,153 ml (range: 45–10,080 ml), and mean red blood cell transfusion was 2.3 ± 4 units (range: 0–36 units).

Postoperative Complications

Table 1 shows postoperative complications after pancreaticojejunostomy. The overall morbidity was 98 (40%). The overall rate of pancreatic fistula was 28% (69 patients). The incidence of pancreatic fistula, as classified by ISGPF, among the 244 patients was grade A in 47 patients (19%), grade B in 17 patients (7.0%), and grade C in 5 patients (2.0%). Nineteen of the enrolled 244 patients (7.8%) had intra-abdominal abscess. Eighteen of the enrolled 244 patients (7.4%) had percutaneous drainage for development of intra-abdominal abscess related to pancreatic fistula after PD. Of 22 patients with clinically relevant pancreatic fistula, 18 had percutaneous drainage, and 1 had a long-term drain placed intraoperatively; the remaining 3 patients received treatment for pancreatic fistula such as administration of antibiotics, total parenteral nutrition, and a protease inhibitor without drainage. The reoperation rate for pancreatic fistula was 0.8% (2 of 244 patients). Two patients required early reoperation because of the presence of peripancreatic effusion that could not be percutaneously drained. Both underwent laparotomy, at which the area was washed extensively and drains were placed.

The mortality rate was 1.6% (4 of 244 patients). One patient died of prolonged liver failure as a result of accompanying liver cirrhosis (preoperative liver damage: B). A second patient died of gastrointestinal bleeding, and a third patient died from septic shock of unknown origin. Amylase level in drainage fluid and radiological findings such as US or CT for this patient did not reveal pancreatic fistula or intra-abdominal abscess. The forth patient died from non-obstructive membrane ischemia.

Table 1 Postoperative complications and outcome after 244 pancreaticoduodenectomies

	No. of patients (%)
Overall morbidity	98 (40)
Local complication	
Pancreatic fistula	69 (28)
Grade A	47 (19)
Grade B	17 (7.0)
Grade C	5 (2.0)
Intra-abdominal abscess	19 (7.8)
Intra-abdominal bleeding	3 (1.2)
Gastrointestinal bleeding	5 (2.0)
Biliary leakage	6 (2.5)
Delayed gastric emptying	23 (9.4)
Wound infection	8 (3.3)
Liver abscess	3 (1.2)
Cholangitis	2 (0.8)
Portal vein thrombosis	1 (0.4)
Systemic complications	
Myocardial infarction	1 (0.4)
Cardiac arrhythmia	1 (0.4)
Pulmonary complications	11 (4.5)
Nonobstructive membrane ischemia (NOMI)	1 (0.4)
Renal failure	1 (0.4)
Management	
Percutaneous drainage[a]	18 (7.4)
Reoperation	2 (0.8)
Mortality	4 (1.6)

[a] Used in postoperative management of intra-abdominal abscess related to pancreatic fistula

Comparison of Patient Characteristics, Intraoperative Status, and Postoperative Outcome

Table 2 shows characteristics, intraoperative status, and postoperative outcome of 244 patients classified by ISGPF. Pancreatic fistula classification was as follows: no pancreatic fistula in 175 of 244 patients (72%), transient pancreatic fistula (grade A) in 47 patients (19%), and clinical pancreatic fistula (grade B + C) in 22 patients (9%). The incidence of soft pancreatic parenchyma or no dilatation of pancreatic duct was significantly greater in patients with pancreatic fistula (grade A or grade B + C) than in those without pancreatic fistula ($P < 0.01$). There were no significant differences between transient pancreatic fistula and clinical pancreatic fistula with regard to patient characteristics and intraoperative status.

As for postoperative outcome, serum albumin level on POD 4 in the grade B + C group was significantly lower than in the grade A group ($P = 0$ .0001), whereas there was no difference in either group on POD 1. On the other hand, leukocyte counts on POD 4 in grade B + C group were significantly higher than those in no pancreatic fistula group and grade A group ($P = 0.008$), whereas there was no difference in either group on POD 1. Although there

Table 2 Characteristics, intraoperative status, and postoperative outcome of 244 patients with pancreaticoduodenectomy as judged by international study group of pancreatic fistula (ISGPF) guidelines

	Pancreatic fistula		
	Not present ($n = 175$)	Grade A ($n = 47$)	Grade B + C ($n = 22$)
Characteristics			
Age	67 ± 10	68 ± 11	72 ± 7
Gender (male/female)	100/75	24/23	13/9
Diabetes (yes/no)	59/116	11/36	5/17
Preoperative serum bilirubin level (mg/dl)[a]	4.0 ± 5.2	2.6 ± 4.0	3.2 ± 4.3
Preoperative biliary drainage (yes/no)	71/104	13/34	9/13
Preoperative serum albumin level (g/dl)[b]	3.9 ± 0.7	4.0 ± 0.4	3.9 ± 0.5
Preoperative serum amylase level (IU/l)[c]	122 ± 180	94 ± 60	94 ± 45
Histology(benign/malignant)	39/136	12/35	3/19
Intraoperative status			
Type of resection (PD/PpPD)	23/152	12/35	4/18
Operative time (min)	366 ± 75	348 ± 63	373 ± 67
Intraoperative bleeding (ml)	1,067 ± 1,207	945 ± 727	1,179 ± 1,453
Red blood cell transfusion (units)	2.4 ± 4.6	1.7 ± 3.1	2.5 ± 4.7
Dilatation of pancreatic duct (yes/no)	107/68	18/29*	4/18**
Pancreatic texture (soft/hard)	59/116	31/16*	17/5**
Postoperative outcome			
Leukocyte counts on POD 1 (mm^{-3})[d]	11,106 ± 3,599	11,955 ± 3,868	11,977 ± 3,754
Leukocyte counts on POD 4 (mm^{-3})[d]	7,964 ± 2,573	9,153 ± 2,682	11,545 ± 2,908[d]
Serum albumin level on POD 1 (g/dl)[b]	3.0 ± 0.4	3.1 ± 0.4	3.0 ± 0.5
Serum albumin level on POD 4 (g/dl)[b]	3.2 ± 0.5	3.3 ± 0.5	2.8 ± 0.2[d]
Amylase level of drainage fluid on POD 1 (IU/l)	1,385 ± 2,679	6,582 ± 9,816*	5,843 ± 9,220**
Amylase level of drainage fluid on POD 4 (IU/l)	86 ± 93	992 ± 1,246*	7,277 ± 15,443**
Percutaneous drainage[e] (%)	0 (0)	0 (0)	18 (82)
Reoperation related to pancreatic fistula (%)	0 (0)	0 (0)	2 (9)
Death related to pancreatic fistula (%)	0 (0)	0 (0)	0 (0)

PD pancreaticoduodenectomy; *PpPD* pylorus-preserving pancreaticoduodenectomy; *POD* postoperative day

[a] Normal range 0.2–1.2 mg/dl

[b] Normal range 3.8–5.1 g/dl

[c] Normal range 15–150 IU/l

[d] Normal range 3,500–9,800 mm^{-3}

[e] Used in postoperative management of intra-abdominal abscess related to pancreatic fistula

* No pancreatic fistula versus grade A $P < 0.01$

** No pancreatic fistula versus grade B + C $P < 0.01$