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(1) TITLE:

Postoperative bowel function and nutritional status following distal pancreatectomy with en bloc celiac axis resection (DP-CAR)

Short title: Bowel function and nutritional status following DP-CAR

(2) AUTHORS:

Satoshi Hirano, MD, Satoshi Kondo, MD, Eiichi Tanaka, MD, Toshiaki Shichinohe, MD, Takahiro Tsuchikawa, MD, Kentaro Kato, MD, Joe Matsumoto, MD

(3) DEPARTMENT AND INSTITUTION:

Department of Surgical Oncology, Division of Surgery, Hokkaido University Graduate School of Medicine, Sapporo, Japan

(4) CORRESPONDING AUTHOR (Reprint requests):

Satoshi Hirano, M.D., Ph.D.

Department of Surgical Oncology, Hokkaido University Graduate School of Medicine, North-15, West-7, Kita-ku, Sapporo 060-8638, Japan

E-mail: satto@med.hokudai.ac.jp

Phone: +81-11-706-7714

Fax: +81-11-706-7158

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Abstract

Background/ Aims: Distal pancreatectomy with en bloc celiac axis resection (DP-CAR) is routinely accompanied by complete resection of the bilateral celiac ganglions and circumferential plexus of the superior mesenteric artery. The postoperative condition including bowel movement and nutritional status, and tolerance to adjuvant chemotherapy has never been studied.

Methods: Forty patients who underwent DP-CAR were enrolled in this study. Postoperative bowel function was estimated by the requirement of antidiarrheal agents. Changes of nutritional parameters including body weight and laboratory data for one year after surgery were evaluated.

Results: Fifteen (38%) patients needed no anti-diarrheal agent after the median follow-up periods of 39 months. Other patients were well controlled for their bowel movement with anti-diarrheal drugs. Thirteen patients who received adjuvant chemotherapy were well tolerated despite the hematologic toxicity in seven patients who received gemcitabine. Postoperative body weight was significantly decreased and reached plateau value at 3 postoperative months. The values of laboratory data indicating nutritional status were significantly dropped at 1 month after surgery and recovered between 3 and 12 months.

Conclusion: The patients who underwent DP-CAR scarcely suffered from intractable diarrhea, and could achieve feasible nutritional status after surgery, to be able to receive adjuvant chemotherapy.

Introduction

Locally advanced cancer of the body of the pancreas frequently involves the common hepatic artery and/or celiac axis with perineural invasion in the nerve plexus surrounding these arteries [1, 2]. Nerve plexus around the superior mesenteric artery which runs below the pancreatic body is often invaded by the tumor either directly or perineurally. We have employed distal pancreatectomy with celiac axis resection (DP-CAR) with en bloc resection of the celiac, common hepatic arteries, and the surrounding nerve tissues such as the celiac plexus, ganglions, and the superior mesenteric plexus [3, 4]. In cancer in the head of the pancreas, the circumferential dissection of the nerve plexus around the superior mesenteric artery during pancreatoduodenectomy with extended lymphadenectomy has made the patients develop severe diarrhea and malnutrition, and resulted in impairment of the postoperative quality of life [5, 6].

Recently, adjuvant chemotherapy using gemcitabine alone [7] or combination with S-1 [8] which is an oral fluoropyrimidine derivative that combines tegafur with two modulators of 5-fluorouracil (5-FU) metabolism, 5-choloro-2,4-dihydroxypyridine and potassium oxonate, have been reported as useful for prolong the patients survival after pancreatectomy for adenocarcinoma. One of the major gastrointestinal toxicities of the gemcitabine or S-1 administration next to anorexia is diarrhea [7, 8]. When the patients develop severe diarrhea and malnutrition after DP-CAR, they could lose the chance to have the adjuvant chemotherapy. Our purpose of this study was to estimate the postoperative defecating condition, nutritional status, and feasibility of adjuvant chemotherapy following DP-CAR.

Patients and Methods

Between August 1998 and July 2008, forty two patients with carcinoma of the body of the pancreas which involved or touched the common hepatic artery, the root of the splenic artery, or the celiac axis, underwent DP-CAR. Informed consent was obtained from all patients. Their ages ranged from 52 to 85 years, with a median of 65 years, and the male/female ratio was 22/20.

The operative procedures routinely included en bloc resection of the celiac, common hepatic, left gastric arteries, the celiac and superior mesenteric plexus, bilateral ganglions. The dissection of the nerve plexus around the superior mesenteric

artery was performed circumferentially from the bottom to the portion immediately proximal to the inferior pancreaticoduodenal artery. A part of the crus of the diaphragm, the Gerota's fascia, the left adrenal gland, the retroperitoneal fat tissues bearing lymph nodes above the left renal vein, the transverse mesocolon covering the body of the pancreas, and the inferior mesenteric vein were also resected with distal pancreas and the spleen. Resection of the portal vein and the middle colic vessels was optional. No reconstruction of the arterial system was required because of early development of the collateral arterial pathways via the pancreaticoduodenal arcades from the superior mesenteric artery had been established by preoperative coil embolization of the common hepatic artery [3, 4]. The whole alimentary tract including the stomach and the biliary system without cancer invasion were preserved. Combined resection of alimentary tract was performed in 9 patients: total resection of the remnant stomach following distal gastrectomy in 2 patients, wedge resection of the stomach in 2 patients, segmental resection of the colon in 2 patients, and wedge resection of the jejunum in 3 patients. Reconstruction of the portal vein was performed in 28 patients.

Post operative condition of bowel function was estimated by the dose and types of antidiarrheal agents. The drugs were prescribed to make the patients have solid or semisolid bowel movement which was no more than approximately 3 times a day instead of diarrhea. Usual dose of pancreatic enzyme supplements (3g/ day of Berizym™ (Shionogi & Co., Ltd, Japan)) were prescribed for all patients. Since 2005, the patients who underwent DP-CAR were recommended to receive adjuvant chemotherapy using gemcitabine or S-1 after discharge. The doses of antidiarrheal agents were compared between before and after receiving chemotherapy.

Serial measurements for one year after surgery of body weight and laboratory data indicating nutritional status were performed in recent 17 patients who had not developed recurrent disease within a year. Serum protein, albumin, and cholesterol levels were selected as parameters reflecting protein-energy malnutrition [9]. Serum hemoglobin levels were measured as a marker of chronic inflammation and as an indicative factor of feasibility of adjuvant chemotherapy. Ten among 17 patients had started to receive adjuvant chemotherapy during serial measurements. Red blood cell transfusions were performed in 4 patients intraoperatively. No patient received either transfusion or drip infusion therapy during the follow-up period.

Out of 16 patients who had suffered diabetes preoperatively, 5 patients got relief

from anti-diabetic treatment. New on-set diabetes after the operation was not encountered.

Data of serial measurements at pre-operative period and at 1, 3, 6, and 12 months after surgery were collected. The data between pre-operative and post-operative periods, and at 1 month and the later periods were compared with Wilcoxon's sign rank sum test using StatViewTM. Probability values less than 0.05 were considered to be statistically significant.

Results

All tumors were diagnosed as ductal adenocarcinoma by histopathologic investigations. According to the International Union Against Cancer (UICC) TNM staging system, stage distribution was 5, 13, 22, and 2 patients for stage IIA, IIB, III and IV, respectively. The R0 operation was achieved in 39 out of 42 patients. Morbidity occurred in 18 patients: pancreatic fistula in 7 and ischemic gastropathy [4] in 5 patients were common. Two patients died with cardiac infarction and multi-organ failure due to anastomotic insufficiency of partial resection of the duodenum within postoperative hospital days, respectively. Except these two, 40 patients were enrolled in the following study. During the study period, recurrence had occurred in 22 patients. The most dominant site of recurrence was liver in 18 patients, whereas the local recurrence was in 4 patients. Median survival time was 24 months and 5-year cumulative survival rate was 25%.

After the median follow-up periods of 39 (range: 3 to 122) months, post postoperative diarrhea was not evident in 15 (38%) patients. Other patients used antidiarrheal drugs as follows; one required tincture of opium, two used albumin tannate combined with natural aluminum silicate, one used Scopolia's extract powder which contains a form of the alkaloid scopolamine, and remnant 21 patients used loperamide hydrochloride (LH). In 21 patients, five used LH occasionally, and remaining 16 used it regularly with the dose of 1 to 6mg/ day (median 3mg)(Table 1).

Out of 19 patients who underwent the surgery since 2005, 13 patients were administrated adjuvant chemotherapy, whereas 5 patients did not hope to have any postoperative treatment, and one patient has been waiting to close duodenocutaneous fistula due to combined resection of total stomach. Adjuvant chemotherapy was started between 25 and 117 postoperative day (median 58 day). A patient who suffered from

postoperative ischemic gastropathy [4] started chemotherapy over 3 months after surgery. Ten of 13 patients were administered gemcitabine ($1000\text{mg}/\text{m}^2$) intravenously with cycle of 4 weeks (infusion in every 3 weeks followed by a week pause). Remnant 3 patients received oral administration of S-1 (80~100 mg/body according to the body weight). In seven patients who received gemcitabine, the cycle of the administration was changed to once for two weeks due to hematologic toxicity. There were no other toxicities which led the patients to discontinue the treatments. The dose of anti-diarrheal agents were increased after beginning of adjuvant chemotherapy in only 3 patients; one was newly started 3mg of LH and two were added the dose of LH from 3 to 6mg.

Serial measurements of the body weight of the patients for a year after surgery revealed significant decreasing until 1 month after surgery and reached plateau value of approximately 14% less than preoperative value after 3 months. The values of serum total protein, albumin, hemoglobin, and cholesterol were significantly dropped at 1 month after surgery. The values of serum total protein and albumin were recovered within 3 months, however, that of cholesterol recovered after 6 months. The value of hemoglobin increased significantly at 6 and 12 months compared to the minimum value at 1 month (Figure 1).

Discussion

In patients who underwent standard distal pancreatectomy, the celiac artery, more than half of plexus of celiac and superior mesenteric artery, and bilateral ganglions are usually preserved. Therefore, no awful disorder of the bowel function such as diarrhea could occur. Contrary to this, DP-CAR includes routine resection of the celiac axis, bilateral celiac ganglions, and the circumferential superior mesenteric plexus. After the operation, as the small intestine loses the extrinsic nerve which regulates its motility, the patients were expected to encounter severe diarrhea. In fact, an experimental study for jejunoileal auto transplantation model of canine shows remarkable shortening of denervated small intestinal transit time in fasting condition [10]. Actually, the most patients who underwent extended pancreatoduodenectomy with the complete resection of the superior mesenteric plexus suffered from intractable and prolonged diarrhea which leads them to severe malnutrition in postoperative days despite of the short survival time [5, 6]. Therefore, the indication of such extended

procedure has been strictly limited. Contrary to expectations, postoperative diarrhea following DP-CAR occurred in 62.5 % of the patients and all except one of them were able to be controlled by using acceptable dose of anti-diarrheal agents without difficulty. Comparing the operative procedures, DP-CAR is different from pancreatoduodenectomy in complete preservation of the duodenum and intestinal continuity. It means that the patients who underwent DP-CAR are more advantageous in digestive and absorptive function than those who underwent pancreatoduodenectomy because secretion of the duodenal hormone such as cholecystokinin and secretin might maintain exocrine function of the remnant pancreas. Additionally, the intrinsic innervation which is preserved by intestinal continuity might regulate the motility of the small intestine [11]. Recently, neuropeptidergic control of small intestinal transit by peptide YY (PYY) released from the distal intestine has been studied. This regulation mechanism which is called ileal brake become activated by ingestion of the nutrients, especially fatty acids, in the distal small intestine and colon, play a role to slow a intestinal transit and help digestion and absorption of the nutrients [12]. Since the release of PYY is revealed to be stimulated by Cholecystokinin [13], in patients who underwent DP-CAR, the brake mechanism of small bowel transit by PYY might be maintained even after the surgery. Regarding the differences in usage of antidiarrheal agents in patients who underwent DP-CAR, no defined explanation could be shown, The differences of pancreatic exocrine function and/ or neuropeptidergic control of intestinal motility of each individuals might cause such differences.

Although the excellent local control of the cancer was achieved by DP-CAR, the postoperative hepatic recurrence has been frequent and problematic [4]. Taking into account the result of randomized controlled trial concerning adjuvant chemotherapy for patients who underwent pancreatectomy for pancreatic cancer [7], we concluded that the patients who underwent DP-CAR should be administrated chemotherapy even after the curative resection. The period from the surgery to beginning of the adjuvant therapy is affected by the postoperative systemic conditions. Especially, postoperative nutritional condition including bowel movement control is one of the important factors to assess the feasibility of chemotherapy after extended gastrointestinal surgery. In this study, the patient`s body weight and value of serum hemoglobin could not return to the preoperative level even at 12 months after surgery. The recovery of the level of serum cholesterol was achieved at 12 months after surgery. The changes of body weight and

the level of cholesterol might be caused by post-operative maldigestion and malabsorption. The decreased level of serum hemoglobin might be affected by intraoperative blood loss, Actually, these data did not delay the commencing time of adjuvant therapy. The patients who received adjuvant therapy in this study could start the treatment within 2 months in median after surgery. They were well tolerated to the chemotherapy except the hematologic toxicity with gemcitabine. Seventy percent of the patients who received adjuvant chemotherapy had to change the protocol. We expect that it could be acceptable as an adjuvant treatment after R0 resection which could not be achieved by performing any operation except DP-CAR.

Preoperative intractable abdominal or back pain is completely diminished due to the resection of bilateral celiac ganglions after DP-CAR [4, 14]. The postoperative bowel movement control and nutritional status, as well as relief of the pain achieve the relatively good quality life after DP-CAR.

In conclusion, despite the persistent loss of the body weight, the patients who underwent DP-CAR scarcely suffered from intractable diarrhea, and could achieve feasible nutritional status within 3 months after surgery, to be able to receive adjuvant chemotherapy.

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Figure legend

Figure 1.

Postoperative changes in various nutritional parameters. (A) Body weight after distal pancreatectomy with en bloc celiac resection (DP-CAR) was significantly lower than that before operation throughout the postoperative course, however reached plateau value of approximately 14% less than preoperative value after 3 months. (B, C, D, and E) Compared with preoperative values, those of serum total protein, albumin, hemoglobin, and cholesterol were significantly decreased at 1 month after surgery. The values of serum total protein and albumin were recovered within 3 months, however, that of cholesterol recovered after 6 months. The value of hemoglobin increased significantly at 6 and 12 months compared to the minimum value at 1 month.

*, $P < 0.05$ compared with the preoperative value; #, $P < 0.05$ compared with the value at one month after surgery; m, month(s)

Table 1. Postoperative usage of anti-diarrheal agent

Frequency of usage	Number of patients
Not used	15
Occasionally used	5
Regularly used	20

Type and dose of agents regularly used

loperamide hydrochloride	16
1mg/day	1
2mg/day	6
3mg/day	6
6mg/day	3
albumin tannate (3g/day) *	2
alkaloid scopolamine (90mg/day)	1
tincture of opium (1.5mL/day)	1

*: used with 3g/ day of natural aluminum silicate

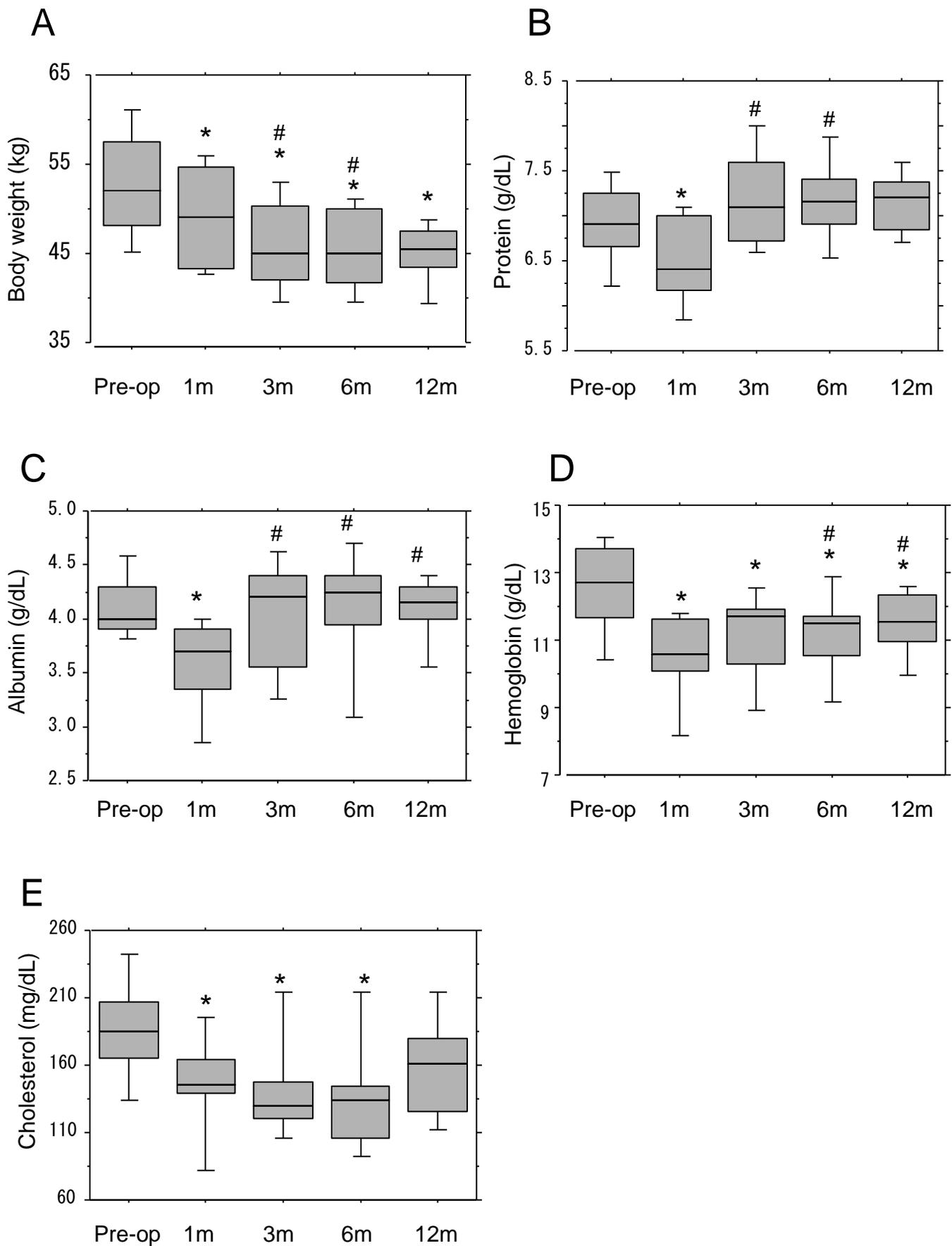


Figure 1