Postoperative Bowel Function and Nutritional Status following Distal Pancreatectomy with En-Bloc Celiac Axis Resection

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Key Words

Pancreatic cancer • Distal pancreatectomy • Postoperative complications • Diarrhea • Nutrition

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 the circumferential plexus of the superior mesenteric artery. The postoperative condition including bowel movement, nutritional status, and tolerance to adjuvant chemotherapy has never been studied. **Methods:** 40 patients who underwent DP-CAR were enrolled in this study. Postoperative bowel function was estimated by the requirement of anti-diarrheal agents. Changes of nutritional parameters including body weight and laboratory data for 1 year after surgery were evaluated. **Results:** 15 (38%) patients needed no anti-diarrheal agent after a median follow-up period of 39 months. The other patients were well controlled for their bowel movement with anti-diarrheal drugs. 13 patients who received adjuvant chemotherapy tolerated it well despite hematologic toxicity in 7 patients who received gemcitabine. Postoperative body weight was significantly decreased and reached a plateau value at postoperative month 3. The values of laboratory data indicating nutritional status were significantly lower at 1 month after surgery and recovered be-

tween 3 and 12 months. **Conclusion:** The patients who underwent DP-CAR scarcely suffered from intractable diarrhea and could achieve a feasible nutritional status after surgery to be able to receive adjuvant chemotherapy.

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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 in 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, has been reported as being useful for prolonging patient survival after pancreatectomy for adenocarcinoma. One of the major gastrointestinal toxicities of gemcitabine or S-1 administration next to anorexia is diarrhea [7, 8]. When patients develop severe diarrhea and malnutrition after DP-CAR, they miss the chance to undergo adjuvant chemotherapy. The 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, 42 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 (median 65) years, and the male:female ratio was 22:20.

The operative procedures routinely included en-bloc resection of the celiac, common hepatic and left gastric arteries, the celiac and superior mesenteric plexus, and 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 pancreatoduodenal artery. Part of the crus of the diaphragm, 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 early development of the collateral arterial pathways via the pancreatoduodenal arcades from the superior mesenteric artery had been established by preoperative coil embolization of the common hepatic artery [3, 4]. The whole alimentary tract was preserved including the stomach and the biliary system without cancer invasion. Combined resection of the alimentary tract was performed in 9 patients: total resection of the remnant stomach following distal gastrectomy in 2, wedge resection of the stomach in 2, segmental resection of the colon in 2, and wedge resection of the jejunum in 3. Reconstruction of the portal vein was performed in 28 patients.

The postoperative condition of bowel function was estimated by the dose and types of anti-diarrheal 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. The usual dose of pancreatic enzyme supplements (3 g/day of Berizym™; Shionogi Co., Ltd., Japan) was 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 anti-diarrheal agents were compared before and after receiving chemotherapy.

Serial measurements for 1 year after surgery of body weight and laboratory data indicating nutritional status were performed in 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. Among 17 patients, 10 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 gained relief from anti-diabetic treatment. New-onset diabetes after the operation was not encountered.

Data of serial measurements in the preoperative period and at 1, 3, 6, and 12 months after surgery were collected. The data between pre- and postoperative periods, and at 1 month and later periods were compared with Wilcoxon's signed-rank sum test using StatView™. $p < 0.05$ was 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 stages 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 in hospital of cardiac infarction and multiorgan failure due to anastomotic insufficiency of partial resection of the duodenum within days postoperatively, respectively. With the exception of these 2 patients, 40 others were enrolled in the following study. During the study period, recurrence had occurred in 22 patients. The most dominant site of recurrence was the liver in 18 patients, whereas in 4 patients it was local recurrence. Median survival time was 24 months and the 5-year cumulative survival rate was 25%.

After the median follow-up period of 39 (range 3–122) months, postoperative diarrhea was not evident in 15 (38%) patients. The other patients used anti-diarrheal drugs as follows: 1 required tincture of opium, 2 used albumin tannate combined with natural aluminum silicate, 1 used Scopolia's extract powder which contains a form of the alkaloid scopolamine, and the remaining 21 patients used loperamide hydrochloride (LH). In 21 pa-

Table 1. Postoperative usage of anti-diarrheal agents

Usage of anti-diarrheal agents	Patients
<i>Frequency of usage</i>	
Not used	15
Occasionally used	5
Regularly used	20
<i>Type and dose of agents regularly used</i>	
Loperamide hydrochloride	16
1 mg/day	1
2 mg/day	6
3 mg/day	6
6 mg/day	3
Albumin tannate (3 g/day) ¹	2
Alkaloid scopolamine (90 mg/day)	1
Tincture of opium (1.5 ml/day)	1
¹ Used with 3 g/day of natural aluminum silicate.	

tients, 5 occasionally used LH and the remaining 16 used it regularly at a dose of 1–6 mg/day (median 3 mg/day) (table 1).

Out of the 19 patients who underwent surgery since 2005, 13 were administrated adjuvant chemotherapy, whereas 5 did not hope to have any postoperative treatment, and 1 patient has been waiting for duodenocutaneous fistula closure due to combined resection of the total stomach. Adjuvant chemotherapy was started between postoperative days 25 and 117 (median 58 days). A patient who suffered from postoperative ischemic gastropathy [4] started chemotherapy more than 3 months after surgery. Of 13 patients, 10 were administrated gemcitabine (1,000 mg/m²) intravenously with a cycle of 4 weeks (infusion in every 3 weeks followed by a 1-week pause). The remaining 3 patients received oral administration of S-1 (80–100 mg according to body weight). In 7 patients who received gemcitabine, the cycle of the administration was changed to once for 2 weeks due to hematologic toxicity. There were no other toxicities which led the patients to discontinue the treatments. The dose of anti-diarrheal agents was increased after beginning adjuvant chemotherapy in only 3 patients: 1 case was freshly started on 3 mg of LH and in 2 cases a dose of 3–6 mg LH was added.

Serial measurements of patients' body weights for a year after surgery revealed a significant decrease until 1 month after surgery and reached a plateau value of approximately 14% less than the preoperative value after

3 months. The values of serum total protein, albumin, hemoglobin, and cholesterol had significantly dropped 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 (fig. 1).

Discussion

In patients who underwent standard distal pancreatectomy, the celiac artery, more than half of the plexus of the celiac and superior mesenteric artery, and bilateral ganglions are usually preserved. Therefore, no adverse 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, in an experimental canine model for jejunoileal autotransplantation, a remarkable shortening of denervated small intestinal transit in the fasting condition was observed [10]. Actually, most patients who underwent extended pancreatoduodenectomy with complete resection of the superior mesenteric plexus suffered from intractable and prolonged diarrhea which led to severe malnutrition in the postoperative days despite the short survival time [5, 6]. Therefore, the indication of such an extended procedure has been strictly limited. Contrary to the expectations, postoperative diarrhea following DP-CAR occurred in 62.5% of the patients and all except 1 subject were able to be controlled by using an acceptable dose of anti-diarrheal agents without difficulty. Comparing the operative procedures, DP-CAR is different from pancreatoduodenectomy for complete preservation of the duodenum and intestinal continuity. This means that the patients who underwent DP-CAR have a better digestive and absorptive function than those who underwent pancreatoduodenectomy, because secretion of the duodenal hormone, such as cholecystokinin and secretin, might maintain the 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 released from the distal intestine has been studied. This regulatory mechanism, which is called the ileal brake, becomes activated by ingestion of

Fig. 1. Postoperative changes in various nutritional parameters. **a** Body weight after DP-CAR was significantly lower than that before operation throughout the postoperative course; however, it reached a plateau value of approximately 14% less than the preoperative value after 3 months. **b–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 1 month after surgery.

the nutrients, especially fatty acids in the distal small intestine and colon, and plays a role in slowing down intestinal transit time and helps digestion and absorption of the nutrients [12]. Since the release of peptide YY is revealed to be stimulated by cholecystikinin [13], in patients who underwent DP-CAR, the brake mechanism of the small bowel transit by peptide YY might be maintained even after surgery. Regarding the differences in usage of anti-diarrheal 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 individual 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 a 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 curative resection. The period from surgery to the beginning of adjuvant therapy is affected by postoperative systemic conditions. Especially the 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 body weight of patients and value of serum hemoglobin could not return to the preoperative level even 12 months after surgery. The recovery of the level of serum cholesterol was achieved 12 months after surgery. The changes of body weight and the level of cholesterol might be caused by postoperative 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 on average start treatment within 2 months after surgery. They tolerated chemotherapy well, except for hematologic toxicity in those treated with gemcitabine. Of

the patients who received adjuvant chemotherapy, 70% had to change the protocol. We expect that it could be acceptable as an adjuvant treatment after R0 resection cannot 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]. With postoperative bowel movement control and nutritional status as

well as relief of the pain, a relatively good quality of life can be achieved 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 a feasible nutritional status within 3 months after surgery to be able to receive adjuvant chemotherapy.

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