Analysis of multiple factors of postsurgical gastroparesis syndrome after pancreaticoduodenectomy and cryotherapy for pancreatic cancer

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AIM: To explore the etiology, pathogenesis, diagnosis, and treatment of postsurgical gastroparesis syndrome (PGS) after pancreatic cancer cryotherapy (PCC) or pancreaticoduodenectomy (PD), and to analyze the correlation between the multiple factors and PGS caused by the operations.

METHODS: Clinical data of 210 patients undergoing PD and 46 undergoing PCC were analyzed retrospectively.

RESULTS: There were 31 (67%), 31/46) patients suffering PGS in PCC group, including 29 with pancreatic head and uncinate tumors and 2 with pancreatic body and tail tumors. Ten patients (4.8%, 10/210) developed PGS in PD group, which had a significantly lower incidence of PGS than PCC group ($\chi^2 = 145, P<0.001$). In PCC group, 9 patients with PGS were managed with non-operative treatment (drugs, diet, nasogastric suction, etc.), and one received reoperation at the 16th day, but the symptoms were not relieved. In PD group, all the patients with PGS were managed with non-operative treatment. The PGS in patients undergoing PCC had close association with PCC, tumor location, but not with age, gender, obstructive jaundice, hypoproteinemia, preoperative gastric outlet obstruction and the type and number of gastric biliary tract operations. The mechanisms of PGS caused by PD were similar to those of PGS following gastrectomy. The damage to interstitial cells of Cajal might play a role in the pathogenesis of PGS after PCC, for which multiple factors were possibly responsible, including ischemic and neural injury to the antopyloric muscle and the duodenum after freezing of the pancreatic-duodenal regions or reduced circulating levels of motilin.

CONCLUSION: PGS after PCC or PD is induced by multiple factors and the exact mechanisms, which might differ between these two operations, remain unknown. Radiotherapy of the upper gastrointestinal tract and gastroscopy are main diagnostic modalities for PGS. Non-operative treatments are effective for PGS, and reoperation should be avoided in patients with PGS caused by PCC.

INTRODUCTION
Postsurgical gastroparesis syndrome (PGS) is a complex disorder characterized by postprandial nausea, vomiting, and gastric atony in the absence of mechanical gastric outlet obstruction. Patients frequently suffer marked weight loss and malnutrition that require hospitalization and prolonged parenteral nutrition (PN). These symptoms can be disabling and often fail to be alleviated by drug therapy, for which gastric reoperations usually prove unsuccessful. An identified cause for PGS has not been available, nor is its mechanism quite clarified. PGS after gastrectomy or pancreaticoduodenectomy (PD) has been reported in a number of literatures[1-5]. Based on the results of clinical investigations[6-9], cryosurgery targeting at the pancreaticoduodenal region was considered safe and effective for unresectable pancreatic cancer. However, PGS caused by cryotherapy for pancreatic cancer (PCC), to our knowledge, has not been reported. As a unique complication of PCC, gastric stasis occurs in the early postoperative period in most of cases receiving PCC (67%), resulting in long-term loss of a large amount of gastric juice and delayed recovery of oral food intake, and occasionally, excessive gastric juice loss leads to body fluid deficit and metabolic alkalosis. To define the factors contributing to the development of PGS following PD or PCC, we performed this study to retrospectively examine the clinical data of 210 patients undergoing PD and 46 undergoing PCC.

MATERIALS AND METHODS
Subjects
From January 1990 to June 2003, 210 patients (147 male and 63 female patients, aged 35 to 75 years with a mean of 53.6 years) received PD in our hospital for pancreatic cancer or periampullary adenocarcinoma. None of the patients were preoperatively identified to have mechanical gastric outlet obstruction, but 95 had obstructive jaundice and 15 had hypoproteinemia.

During the period between January 1995 to March 2003, another 46 patients (including 31 male and 15 female patients, aged between 39 and 78 years with a mean of 54 years) underwent PCC for unresectable advanced pancreatic cancer, located in the pancreatic head in 21 cases, in the uncinate process in 15 cases, and in the pancreatic body and tail in 10 cases. All the tumors were identified by preoperative helical computed tomography (CT) scan and by intraoperative exploration, including 31 tumors with local involvement and 15 metastatic tumors. Preoperatively, 34 patients were identified to have obstructive jaundice and 6 had hypoproteinemia. All the patients, excluding the 8 with preoperative duodenal obstruction, were free of preoperative mechanical gastric outlet obstruction. Gastrojejunostomy was performed in 37 cases, and cholecystojunostomy or choledochojejunostomy done in 32 cases during PCC for relief or prevention of the common bile duct and gastric outlet obstruction. Four patients also had concurrent splanchicectomy with ethanol.

Endoscopy or radiography was employed to identify and exclude cases of mechanical gastric outlet obstruction, and also to detect such problems of Anastomotic stricture, efferent
limb obstruction, and jejunogastric intussusception etc., as well as food retention after a 4- to 8-h fast, for validating the diagnosis of gastroparesis.

**Diagnostic criteria for PGS**

At present, consensus has not been reached on the criteria for diagnosis of PGS. Staniciu[5] suggested using gastric scintigraphy with 99mTc-labeled low-fat meal as the gold standard for diagnosing delayed gastric emptying, which utilized gamma camera imaging of the abdomen following the ingestion of a radiolabeled meal, performed at regular intervals of 2 to 4 h to quantify the meal emptying in terms of percentages. Typically, meal emptying of over 50% within 2 h was considered normal, whereas delayed gastric emptying was indicated if gastric retention greater than 10% at 4 h. In this study, we formulated practical diagnostic criteria for PGS after consultation of the previous documentations in the literature[3-7,10], as the following: (1) Absence of mechanical gastric outlet obstruction identified by one or more medical examination modalities; (2) A volume of gastric juice aspirate exceeding 800 mL/d that sustained for more than 10 d; (3) No abnormalities in water, electrolytes, or acid-alkali balance. (4) Absence of underlying diseases causing gastroparesis, such as diabetes, cholecystitis, hypothesis, etc. (5) No history of using such agents as morphine, atropine, etc. that affected contraction function of the smooth muscle.

**Surgical procedures**

In PD group, the organs resected during PD included the gallbladder, common bile duct, head of the pancreas, the entire duodenum, with also subtotal gastrectomy. Proximal jejunum of 10 to 15 cm was also resected. The alimentary and biliary tracts were reconstructed with methods of Child or Whipple.

In patients of PCC group that defined surgical resection of the tumor, cryoprobes were deployed directly into the tumor for freezing to -196 °C twice, lasting for 10-15 min (using LCS 2000 cryogenic surgical system), with the common bile duct, stomach, and jejunum protected by dry cotton pads. Subsequent gastroenteroanastomosis, cholecystojejunostomy, or choledochojejunostomy were performed to reconstruct the alimentary and biliary tracts, according to the findings by intraoperative exploration. Care was taken to avoid freezing of the duodenal wall or causing other iatrogenic injuries such as damage to the biliary system or gastroduodenal artery. Jejunostomy was performed in some cases highly suspected of gastroparesis after PCC for postoperative enteral nutrition (EN) support.

**Statistical analysis**

The incidence of PGS in the two groups was compared and multiple factors were analyzed using χ2 test. A P value less than 0.05 was considered statistically significant.

**RESULTS**

No serious complications took place in the PCC group, nor did operative death or complications occur in relation to the anastomosis. None of the patients developed fistula or pancreatitis. There was only transient elevation of amylase following the operation and the liver function and blood sugar remained normal. In PD group, in contrast, 4 patients developed serious complications after PD, including leakage at the pancreatic jejunostomy in 2, bleeding at the anastomosis in 2 cases, stenosis of the anastomosis in 1 and stress peptic ulcer in 1 case. The mortality rate of PD in the perioperative period was 1.5%.

Ten of the 210 patients in PD group presented PGS within 5-10 d postoperatively. PGS developed in 31 of the 46 patients in PCC group, occurring within 5-7 d after the operation, including 29 patients with pancreatic body and tail tumors and 2 with pancreatic body and tail tumors. In PD group, 14 patients with PGS received non-operative treatment such as medication, diet therapy, and nasogastric suction etc. and 1 patient underwent reoperation on postoperative day 16, which, however, failed to relieve the symptoms. All patients with PGS in PCC group received non-operative treatment. Altogether 41 patients developed PGS in the two groups according to our diagnostic criteria, 15 of these cases were identified 4-7 d after withdrawal of the nasogastric tube and 10 were found to have a gradually increasing volume of gastric juice aspirate to 800 mL/d till 3-7 d after operation. Twenty of the 40 patients developed PGS 2-3 d after intake of liquid or semiliquid diet. Furthermore, the volume of gastric juice suction exceeded 2 000 mL/d in 4 cases following PCC and persisted for ten or more days (Table 1).

PGS following cryosurgery was closely associated with PCC, tumor location, but not with age, gender, obstructive jaundice, hypoproteinemia, preoperative gastric outlet obstruction or the type and number of gastric biliary tract operations (Table 2). PGS following PD was related with age, hypoproteinemia, preoperative gastric outlet obstruction and the type and number of gastric operations performed. Patients undergoing PCC were more likely to develop PGS than those undergoing PD (67% vs 4.8%, χ2 = 145, P<0.001).

**DISCUSSION**

Many debates over the etiology and pathophysiology of PGS remain unresolved. Clinically, the frequency of this complication varies in close association with the type and number of gastric operations performed. Donahue et al.[11] reported a 26% incidence of chronic morbidity in patients after truncal vagotomy and antrectomy compared with a 5% incidence after highly selective vagotomy. There also appears to be a greater incidence of PGS associated with antrectomy and Roux-en-Y reconstruction compared with more conventional Billroth I and Billroth II reconstructions. Therefore, the main factor contributing to PGS is denervation and the consequent atony of the gastric remnant rather than disruption of the pacemaker activity in the Roux limb.

The exact mechanisms responsible for PGS after gastric surgery remain unclear but are likely to be multifactorial. The loss of gastric parasympathetic control resulted from vagotomy contributes to PGS via several mechanisms. In the proximal stomach, loss of vagal control leads to accelerated emptying of liquids by disrupting the late-stage tonic contractions responsible for relaxation and accommodation of the gastric fundus. In the distal stomach, vagotomy weakens antral peristaltic contraction responsible for breakdown of chyme. When coupled with the observed decrease in intestinal secretion of prokinetic hormones seen after truncal vagotomy, this leads to delayed emptying of solid substances. Also, the loss of vagal suppression of the ectopic intestinal pacemakers may cause dissociation of the antral pressure waves from the duodenal waves. The consequent disruption of wave sequence prolongs the lag phase of solid food digestion during which food is broken down into small particles by retroperfusion and further delays the digestive process[12,13].

Recently, it has been recognized that interstitial cells of Cajal generate electrical pacemaker activity and mediate motor neurotransmission in the stomach. The interstitial cells of Cajal are located in the muscular wall of the gastric corpus and antrum. Gastric dysrhythmias (tachygastrias and bradygastrias) are disturbances of the normal gastric pacemaker potentials and are associated with such symptoms as nausea, epigastric fullness, bloating and delayed gastric emptying. Ordog et al.[14] suggest that damage to interstitial cells of Cajal may play a key role in the pathogenesis of diabetic gastropathy. Meanwhile, Zarate et al.[15] reported that histological and immunohistochemical
study of the resected specimen showed hypoganglionosis, neuronal dysplasia, and marked reduction in both myenteric and intramuscular interstitial cells of Cajal in patients with idiopathic gastroparesis.

Certainly, PGS after gastric surgery also can be due to muscular, neural, or humoral abnormalities. Hypothyroidism and diabetes\(^4\) have been identified as contributing factors to gastroparesis in some patients. In patients without an identified cause, the gastroparesis is labeled as idiopathic. The mechanisms of PGS following PD is similar to that after gastrectomy.

### Table 1 Clinical data of the PGS cases

| Patient No | Gender | Age (yr) | Operation type | Mean volume of gastric juice aspirate/d (mL) | Period of nasogastric tube aspirate(d) | Period of recovery (d) | Outcome |
|------------|--------|----------|----------------|---------------------------------------------|--------------------------------------|------------------------|---------|
| 1          | M      | 53       | PCC+A+B        | 2 200                                       | 56                                   | 70                     | Recovery |
| 2          | F      | 39       | PCC+B          | 1 200                                       | 13                                   | 28                     | Recovery |
| 3          | F      | 62       | PCC+A+C        | 1 000                                       | 10                                   | 14                     | Recovery |
| 4          | M      | 60       | PCC+A+C        | 1 000                                       | 21                                   | 21                     | Recovery |
| 5          | M      | 51       | PCC+A          | 850                                         | 10                                   | 30                     | Recovery |
| 6          | M      | 61       | PCC+A+B        | 1 250                                       | 15                                   | 26                     | Recovery |
| 7          | M      | 62       | PCC+A+C        | 1 200                                       | 13                                   | 35                     | Recovery |
| 8          | F      | 60       | PCC+C          | 1 300                                       | 11                                   | 43                     | Recovery |
| 9          | F      | 40       | PCC+A+B        | 2 000                                       | 25                                   | 25                     | Recovery |
| 10         | F      | 61       | PCC+A+C        | 1 200                                       | 19                                   | 14                     | Recovery |
| 11         | M      | 64       | PCC+A+B        | 1 200                                       | 18                                   | Death on d 13 for diabetes complication | Death |
| 12         | F      | 78       | PCC            | 1 500                                       | 19                                   | Discharged on d 24\(^2\) | Recovery |
| 13         | M      | 50       | PCC+A+C        | 1 050                                       | 12                                   | 49                     | Recovery |
| 14         | M      | 50       | PCC+A+C        | 1 400                                       | 15                                   | Discharged to another hospital on d 16 | Recovery |
| 15         | M      | 42       | PCC            | 1 450                                       | 17                                   | 14                     | Recovery |
| 16         | M      | 46       | PCC+A+C        | 2 000                                       | 18                                   | 21                     | Recovery |
| 17         | M      | 43       | PCC+A+B        | 1 200                                       | 13                                   | 20                     | Recovery |
| 18         | M      | 73       | PCC +B         | 800                                         | 10                                   | 19                     | Recovery |
| 19         | M      | 46       | PCC            | 1 350                                       | 14                                   | 18                     | Recovery |
| 20         | M      | 62       | PCC+A+B+D      | 900                                         | 11                                   | 19                     | Recovery |
| 21         | M      | 40       | PCC+A+C        | 1 300                                       | 15                                   | 20                     | Recovery |
| 22         | F      | 50       | PCC +C         | 2 050                                       | 24                                   | 32                     | Recovery |
| 23         | F      | 61       | PCC+A+C        | 1 200                                       | 15                                   | 20                     | Recovery |
| 24         | M      | 39       | PCC+A+B        | 1 000                                       | 12                                   | 14                     | Recovery |
| 25         | M      | 53       | PCC+A          | 1 050                                       | 13                                   | 17                     | Recovery |
| 26         | F      | 42       | PCC+A+B        | 900                                         | 11                                   | 18                     | Recovery |
| 27         | M      | 60       | PCC+A+C        | 1 800                                       | 19                                   | 25                     | Recovery |
| 28         | M      | 62       | PCC            | 1 700                                       | 20                                   | 30                     | Recovery |
| 29         | M      | 60       | PCC+A+C        | 1 050                                       | 12                                   | 20                     | Recovery |
| 30         | M      | 40       | PCC+A+C        | 1 250                                       | 12                                   | 17                     | Recovery |
| 31         | F      | 64       | PCC+A+B        | 1 300                                       | 13                                   | 31                     | Recovery |
| 32         | M      | 75       | PD             | 1 200                                       | 12                                   | 16                     | Recovery |
| 33         | F      | 42       | PD             | 850                                         | 10                                   | 15                     | Recovery |
| 34         | F      | 35       | PD             | 1 050                                       | 10                                   | 19                     | Recovery |
| 35         | M      | 45       | PD             | 1 250                                       | 11                                   | Death on d 16 for complications | Death |
| 36         | F      | 48       | PD             | 1 050                                       | 11                                   | 17                     | Recovery |
| 37         | M      | 56       | PD             | 1 450                                       | 16                                   | 21                     | Recovery |
| 38         | M      | 60       | PD             | 1 400                                       | 14                                   | 20                     | Recovery |
| 39         | F      | 65       | PD             | 1 500                                       | 15                                   | Reoperation at 16th d | Recovery |
| 40         | M      | 47       | PD             | 1 250                                       | 13                                   | 18                     | Recovery |
| 41         | M      | 63       | PD             | 1 600                                       | 16                                   | 21                     | Recovery |

mean±SD 53.8±13 1 180±310 15.5±6 23.1±9

A: Gastroenteroanastomosis; B: Cholecystojejunosotomy; C: Choledochojejunosotomy; D: Chemical splanchnicectomies. 1Discharged on request by the patient.
The results of our observations suggest no significant direct relation of PGS following PCC with the types of gastric operations or the loss of gastric parasympathetic control, nor was it related to the patients’ age or presence of hypoproteinemia or preoperative gastric outlet obstruction (Table 2), which, however, might be the factors contributing to PGS after gastrectomy or PD[1-5]. We therefore suggest that the mechanism of PGS after PCC may differ, at least partially, from that underlying the PGS following gastrectomy or PD.

Patients with tumors located in the pancreatic head and antropyloric muscles and the duodenum after freezing of the pancreatico-duodenal area (but not to direct freezing of the antropyloric muscles and the duodenum) may be one of the several possible causes of PGS after PCC. But still, the above hypotheses currently have to remain hypothetical, and the exact mechanisms of PGS caused by PCC must await further investigation.

Patients with PGS have non-specific symptoms of early satiety, postprandial bloating, nausea, and vomiting, and the volume of gastric juice suction in most of them can increase gradually during early postoperative period. The diagnosis of PGS is often difficult to confirm. In the absence of identifiable anatomic problems such as anastomotic stenosis, efferent limb obstruction, or jejuno gastric intussusception, other causes of gastric dystonia must be carefully examined. Hypothyroidism has been identified as a contributing factor to gastroparesis in some patients. Gastroparesis can also occur in patients with diabetes[18,19]. Several complementary diagnostic modalities may be used to confirm the diagnosis of PGS. Fiberoptic endoscopy or radiography of the upper gastrointestinal tract should be performed routinely to exclude anatomical causes of gastric outlet obstruction. Radionuclide GESs can also be necessary, for clinical evaluation and conventional radiographic studies are often unreliable. If endoscopy and radionuclide scintigraphy are inconclusive, a small bowel contrast study should be performed to rule out possible mechanical lesions and/or generalized gut hypomotility. Although not routinely available[20], electromyography of the gastrointestinal tract may provide valuable assistance in the diagnosis of patients with complex motility disturbances.

As the treatment of gastroparesis is far from ideal, nonconventional approaches and nonstandard medications might be of use. Traditional medical therapy consists of behavioral and diet modification, nasogastric tube suction and the use of prokinetic drugs such as bethanechol, metoclopramide, erythromycin and the more recent cisapride[10]. Dietary measures and prokinetic drugs may help relieve the symptoms in most patients, while some patients with severe nausea and vomiting require antiemetic medications. A few patients fail medical therapy and continue to have debilitating symptoms of gastroparesis, who may benefit from a venting gastrostomy[10] or jejunostomy performed surgically, endoscopically, or fluoroscopically[20]. Near-completion gastrectomy (NCG) has proved useful in small series of patients[21], but data on long-term follow-up has been lacking. Gastric electrical stimulation can be of value in the management of gastroparesis[21-24], in which the patients with PGS received continuous high-frequency/low-energy gastric electrical stimulation via electrodes deposited in the muscular wall of the antrum and connected to a neurostimulator in an abdominal wall pocket. This method produced entrainment of the intrinsic slow wave and promoted contractions in phase III with the normal slow wave. This is why a suitable stimulation to the stomach during gastroscopic examination is also helpful for the remission of PGS[11-5]. In this study, 5 patients received gastroscope examination and the symptoms were markedly relieved. Ten patients with PGS were treated with acupuncture, and the effects were satisfactory.

According to our experience, all patients of PGS caused by PD or PCC need to undergo a long period of nasogastric suction till the clinical symptom relief or recovery occurs. The patients may experience epigastric fullness, nausea, or even vomiting, if
the nasogastric tube is withdrawn too early. Therefore, almost all of the patients with PGS in this study received the gastric juice suction over an average period of 2.2 wk, with the longest exceeding 8 wk. Because of long-term absence of food intake, these patients required nutritional support with a feeding jejunostomy tube or underwent a period of parenteral nutrition. The jejunostomy tube, as we believe, is safe, economic and practical for nutrition support in such patients, because their small intestinal peristaltic contractions and absorption function were normal in spite of PGS. Clinically, almost all of the patients had a concurrent jejunostomy during cryosurgery, considering the likeliness of these patients to develop delayed gastric emptying and for administration of postoperative enteral nutrition support. We consider that the non-operative treatments are effective for PGS after PCC or PD, and gastric reoperations should be avoided.

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