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Review

Enteric reconstruction of pancreatic stump following pancreaticoduodenectomy: A review of the literature

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ABSTRACT

Techniques for reconstruction of pancreatic stump with gastrointestinal tract following pancreaticoduodenectomy are closely related to postoperative complications, mortality and quality of life. In order to reduce postoperative complications, particularly pancreatic fistula, many modifications and new surgical techniques have been proposed to replace the traditional pancreaticojejunostomy and pancreaticogastrostomy. The objective of this review, based on large prospective randomized trials and meta-analyses, is to evaluate the different techniques of enteric reconstruction of pancreatic stump following pancreaticoduodenectomy, including: invagination pancreaticojejunostomy, binding pancreaticojejunostomy, duct-to-mucosa pancreaticojejunostomy, Roux-en-Y pancreaticojejunostomy, and pancreaticogastrostomy, so as to provide a comprehensive comparison of these techniques and to assess of their roles and effectiveness.

1. Introduction

The first successful pancreaticoduodenectomy (PD) was performed by Walther Kausch in 1909 as a two-step procedure. The digestive tract reconstruction consisted of pancreaticoenterostomy and gastroenterostomy via a proximal jejunal loop, with side-to-side anastomosis between the distal jejunum and gallbladder, and side-to-side anastomosis between the proximal and distal jejunum. In the old days, PD had not been widely used due to its complexity as well as the long operative duration. Until 1935, the American surgeon Allen Whipple performed a similar technique of resection, and refined the technique into a one-step operation in 1941, which has since been considered as the starting point for a truly modern era of PD. The sequence of digestive tract reconstruction used by Whipple was in the order of bile duct, pancreas, stomach and jejunum. This has since been called the Whipple procedure [1]. In 1944, Charles Child proposed a new method of reconstruction, namely an anastomosis between the jejunal and pancreatic stump, end-to-side anastomosis of the common bile duct and jejunum, and end-to-side anastomosis of the stomach and jejunum, or in the sequence of pancreas, bile duct, stomach, and jejunum. This has since been known as the Child's operation [2]. At around the same time, in 1943, Cattel designed a refinement of the operation which consisted of an end-to-end anastomosis between the proximal jejunal stump and stomach, end-to-side anastomosis between the pancreas and jejunum, and end-to-side anastomosis between the bile duct and intestine, or the stomach-pancreas-bile duct-jejunum sequence, which is termed the Cattel's method. The Whipple procedure, Child's operation, and Cattel's method are three traditional techniques for digestive tract reconstruction after PD. The Child's operation has a low likelihood of pancreatic stimulation by bile and a low occurrence of cholangitis in the event of regurgitation of food, and is considered a classical method for digestive tract reconstruction following PD.

Evaluating the suitability of digestive reconstruction techniques requires understanding of the occurrence and severity of post-operation complications which mainly include pancreatic fistula (POPF), bile leakage, hemorrhage, and delayed gastric emptying (DGE). With recent advances in surgical technique and perioperative management, the operative mortality rate of PD dropped dramatically in the last two decades to less than 5% in many centers [3–9]. Despite reductions in mortality after PD, the incidence of

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postoperative morbidity remains high, which ranges between 30% and 50% [10,11]. The POPF rate ranges from 5% to 40%, even in specialized centers and depending on the definitions used [8,12]. The rate does not seem to decline in the same way as the mortality rate has done over the last few decades [13–15]. Hemorrhage and sepsis are the most frequent sequels of POPF, both of which contribute largely to mortality (20%–40%) as well as to prolonged hospitalization and increased hospital cost [4,16,17]. The rate of hemorrhage is approximately 0–25% [18,19], and that of DGE is 7–37% [20,21].

Among the complications, POPF remains a major cause of postoperative morbidity, and it contributes significantly to mortality [11]. In an attempt to prevent post-operation complications, especially POPF, many refinements of procedures have been proposed. In the past 30 years, over 50 types of pancreatic and digestive tract reconstruction techniques have been reported. The increase in techniques of pancreatic and digestive tract reconstruction reflects the pancreatic surgeons' continuous efforts to reduce complications of pancreatic surgery, who aim to refine pancreatic and digestive tract reconstruction so as to develop a better anastomotic method to reduce complications after PD. On the other hand, the emergence of a variety of surgical methods indicates that there is currently no perfect method. The best pancreatic anastomosis technique after PD is still under debate.

2. Methods for restoration of pancreatico-enteric continuity

When PD was initially performed, the most common management of the residual pancreas was ligation of the main pancreatic duct and suturing of the pancreatic stump without doing any anastomosis. It has been demonstrated that pancreatic juice leakage at the pancreatic stump occurred easily following ligation of the main pancreatic duct, followed by gradual atrophy of the pancreas, complete loss of endocrine and exocrine function, postoperative diabetes, and reduced quality of life. As a consequence, this method has been abandoned. In 1909, invagination pancreaticojejunostomy (IPJ) was first studied in canine models [22]. In 1941, IPJ was first used clinically for the management of pancreatic stump following PD. With preserved pancreatic function and reduced POPF, this modification provided the theoretical and practical evidence to support the use of PJ [23]. In the Whipple procedure, Child's operation, and Cattel's method, enteric reconstruction of pancreatic stump is pancreaticojejunostomy. The basic types of PJ evolved subsequently to include invagination, binding, and duct-to-mucosa anastomoses.

3. Pancreaticojejunostomy (PJ)

3.1. Invagination pancreaticojejunostomy (IPJ)

IPJ is performed by invagination of the pancreatic stump into the intestine in either an end-to-end or an end-to-side manner. For the convenience of performance, no requirement for identification of main pancreatic duct, and in accordance with physiological structure of digestive tract, IPJ has been considered as the conventional and classic anastomosis method from the origin of PD and is the most common type of PJ used nowadays. The incidence of postoperative complications has also been regarded as standard for evaluation of different techniques.

As reported in many publications, the POPF rate varies greatly in different reports in patients underwent IPJ because of variations in definitions used. In a review by Bassi et al. [9], the incidence ranged between 9.9% and 28.5%, and the different definitions used in pancreatic leakage resulted in highly significant differences between them. Other complications often happen after the onset of POPF. Postoperative bleeding due to erosion of peripancreatic vessels by extravasated pancreatic juice has been described in 2–8% of cases [16,24,25]. The morbidity rate increased from 6% to 26% when POPF became manifested [4,26,27].

In devising a reliable pancreaticoenteric anastomosis, different pancreaticojejunal invagination techniques have been proposed: including the inverting IPJ, the dentate inter-locking PJ, and the double-layer continous IPJ. Among these refinements of PJ, several modified techniques have been reported to give very good results. One is the "Transpancreatic U-sutures IPJ" developed by Chen XP et al. [28] which presents a new technique of the end-to-end IPJ with two to three transpancreatic U-sutures, the POPF caused by needle penetrates was decreased through reducing the suture in pancreatic parenchyma and ductile. In 88 patients who underwent this Transpancreatic U-sutures IPJ PD, only 2 patients (2.2%) developed a grade A POPF. This refinement was widely considered as the first proponent for the principle of superabundant suture in pancreas leading excess POPF. Similarly, Chen HW et al. [29] developed a "pulling IPJ". In their cohort study on 52 consecutive patients, the POPF rate was 0%. Recently, Nakanishi Y et al. [30] reported on the "Four sutures IPJ" with a 0% grade B or C pancreatic fistula rate in 15 consecutive patients who underwent PD.

In so far as end-to-end and end-to-side procedures, there were few randomized comparative trials which have been reported to compare these two methods [31]. A prospective study involving 295 consecutive patients who underwent PD showed end-to-end PJ resulted in more complications than end-to-side PJ ($p = 0.0046$) [32]. Based on limited evidence, it is still unclear which PJ technique is superior and there is not enough evidence to draw any conclusions.

3.2. Binding pancreaticojejunostomy (BPJ)

Peng et al. proposed that pancreatic fistula starts at a point where a needle inadvertently penetrates a pancreatic ductule or a suture lacerates the fragile pancreatic parenchyma on suturing or tying a knot. The resultant minor leak in pancreatic juice gradually leads to gross leakage as a consequence of autodigestion around the anastomosis. Based on this hypothesis, Peng et al. [33] described a BPJ technique in 2004. From 1996 to 2003, 227 consecutive patients underwent BPJ, with none of the patients developing pancreatic anastomotic leak [16]. This favorable outcome was further validated in their own RCT [34]. Of 111 patients randomized to the conventional pancreaticojejunostomy (CPJ) group, POPF occurred in 7.2%, while none of the 106 patients randomized to the BPJ group developed POPF ($p = 0.014$). Postoperative complications developed in 36.9% of the patients in the CPJ group, compared with 24.5% in the BPJ group ($p = 0.048$). The mortality rate was 6.3% in the perioperative period in the CPJ group when compared with 2.8% in the BPJ group ($p = 0.37$). The pancreatic consistency was well-balanced in both groups; therefore, Peng concluded that BPJ can be safely performed even for cases with a soft pancreatic texture. Three prospective studies indicated that BPJ is a safe and secure technique that decreases the rate of POPF formation (8.9% by Buc [35], 3.0% by Nordback [36] and 0% by Hashimoto [37]).

However, no repeatable RCT data about BPJ except Peng's was reported in other centers which probably results from the technical limitations of BPJ itself. First, the tension of binding is hard to control. Too tight binding may cause necrosis, resulting in severe POPF, while too loose binding may not impede pancreatic juice leakage. This problem was recently verified by Casadei et al. [38] who demonstrated that in European population, BPJ according to Peng did not preclude or reduce POPF rate. Second, the jejunal mucosa is difficult to suture. If the mucosa is destroyed, vascularization of anastomosis is compromised; if the mucosa is completely intact the pancreatic stump may be exposed to pancreatic juice, which may

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lead to bleeding at the anastomotic site. Third, BPJ was originally performed in an end-to-end manner [33,34,39]. This technique may not be completed when the intestine is too small or the pancreatic stump is too large to invaginate the pancreatic stump into the jejunum. Therefore, further well-designed, large-volume studies are required to accumulate evidence to draw conclusion.

3.3. Duct-to-mucosa pancreaticojejunostomy (DmPJ)

DmPJ was first performed by Varco in 1945 [40]. The classical duct-to-mucosa technique can be considered to be a two-layer anastomotic technique, with the inner layer consisting of suturing of Wirsung's duct to jejunal mucosa. DmPJ allows for tight adhesion between the pancreatic stump and intestinal wall, enabling rapid and close adherence due to absence of effusion, and rapid anastomotic patency and exocrine function [41]. In addition, DmPJ does not take into account the size of the residual pancreas, eliminating the problem of too loose or too tight invagination. Eversion of intestinal mucosa with its accompanying mucosal destruction is not required, as in BPJ. Due to these benefits, DmPJ is considered to be safe with a low incidence of pancreatic leak [42,43] and has been used for a long time. However, dead space may exist between the pancreatic stump and jejunal wall, resulting in retention of pancreatic juice from the accessory or tiny pancreatic ducts. Furthermore, if the Wirsung's duct has a small diameter, DmPJ is difficult and the anastomosis is likely to obstruct.

Duct-to-mucosa and invagination are two classical PJ techniques. Many studies have compared these two techniques, but the results are difficult to interpret because these studies involved different definitions of pancreatic fistula, heterogeneous methodological trial designs, varying surgical skills and various combinations of other auxiliary treatments. To date, five RCTs have been published to compare DmPJ and IPJ (Table 1). Of the five RCTs, Berger et al. [44] reported an increased risk of POPF with duct-to-mucosa anastomosis while others reported no difference in the risk of POPF [45,46,57].

Bai et al. [48] performed a meta-analysis to compare the duct-to-mucosa and invagination techniques of PJ. Of 321 abstracts, there were 4 relevant RCTs with 467 patients being included (duct-to-mucosa: 232; invagination: 235). POPF rate, mortality, morbidity, reoperation and hospital stay were similar between the two techniques. The authors concluded that given the heterogeneity and probable publication bias, DmPJ was not better than IPJ in patients who underwent PD. But a valuable feature is that a low incidence of pancreatic fistula was found in low-risk patients with pancreatic duct dilation of over 3 mm and pancreatic fibrosis who underwent DmPJ. End-to-end IPJ was safer in high-risk patients with small pancreatic ducts and soft pancreatic parenchyma [28].

4. Pancreaticogastrostomy (PG)

In the hope of overcoming the high incidence of complications after PJ, the first PG was performed by Waugh and Clagett in 1946 [49]. Oida [50] advocated three major benefits associated with PG: First, the stomach has a thick wall and abundant blood flow; Second, the pancreatic remnant exits close to the dorsal side of the stomach; Third, there is no enterokinase expression in the stomach, so pancreatic enzymes will not be activated. This hypothesis was first confirmed by a meta-analysis conducted by McKay et al. [51] based on 11 clinical observations which revealed a lower incidence of pancreatic fistula, overall complications, and mortality rate for PG when compared with PJ. A recently published multicenter study [52] demonstrated that the overall incidence of postoperative complications did not differ significantly between PJ and PG. However, in patients undergoing PD for pancreatic head or periampullary tumors, PG was more efficient than PJ in reducing the incidence of POPF. Based on these advantages, PG was widely accepted to be superior to PJ for many years.

However, most of the studies McKay et al. used were cohort studies. Taking into consideration that gastric acid easily erodes pancreatic stump, ultimately inducing an anastomotic fistula, whether PG was superior or inferior to PJ remained controversial. Between May 1993 and November 1995, a large prospective trial was conducted at the Johns Hopkins. This first prospective clinical trial by Yeo et al., in 1995 [53], showed no difference between the 2 methods with regards to postoperative complications. In 2005, a randomized controlled trial of 151 patients with soft pancreas with a duct diameter of less than 5 mm demonstrated similar rates of pancreatic fistula, but higher biliary fistulae and peritoneal effusions in the PJ group when compared with the PG group [54]. Another level 1 evidence also demonstrated similar rates of pancreatic fistula, biliary fistula, peripancreatic effusion, and surgical mortality, as well as quality of life when comparing PG and PJ [55].

From 2013 onwards, there have been 7 RCTs, 22 observational clinical studies (OCSs) and 27 meta-analyses which compared complication rates between PG and PJ. Among the 7 RCTs studies (Table 2), 3 RCT studies reported by Fernández-Cruz et al. [56], Topal et al. [57] and Figueras J et al. [58]showed that the incidence of POPF was significantly higher following PJ than PG, as was the severity of pancreatic. The hospital readmission rate for complications was significantly lower after PG, weight loss was lower and exocrine function better ($P = 0.022$). The rate and severity of POPF was significantly lower with the PG technique than PJ. On the other hand, the remaining 4 randomized controlled trials revealed a significant difference between PJ and PG with regard to intra-abdominal fluid collections ($p = 0.005$), but without any significant differences in pancreatic fistula, overall postoperative complications, delayed gastric emptying, and mortality rates.

A recent meta-analysis [59] showed PG had significantly lower rates of postoperative intra-abdominal fluid collection ($p = 0.003$) and multiple intra-abdominal complications ($p = 0.0007$) than PJ in 4 RCTs. Twenty-two observational clinical studies demonstrated significant differences between PG and PJ in frequencies of postoperative biliary fistula, intra-abdominal fluid collection,

Table 1
RCTs comparing DmPJ and IPJ.

Reference	Pancreatic fistula (%)	Morbidity rate (%)	Mortality rate (%)
Chou et al., 1996	2 vs. 7	13 vs. 21	3 vs. 4
Bassi et al., 2003	13 vs. 15	54 vs. 53	2 vs. 0
Langrehr et al., 2005	2 vs. 2	40 vs. 38	0 vs. 0
Berger et al., 2009	23 vs. 12[a]	53 vs. 49	2 vs. 0
Han et al., 2009	2 vs. 6	9 vs. 15	1 vs. 1

[a] <0.05.

Table 2
RCTs – PG versus PJ.

Study	POPF rate (%) (PG vs. PJ)	Morbidity rate (%)	Mortality rate (%)
Yeo et al., 1995	12 vs. 11	49 vs. 43	0 vs. 0
Duffas et al., 2005	16 vs. 20	46 vs. 47	12 vs. 10
Bassi et al., 2005	13 vs. 16	29 vs. 39	0 vs. 1
Fernández et al., 2008	4 vs. 18*	23 vs. 44*	
Wellner et al., 2012	10 vs. 12	N/A	2 vs. 2
Topal et al., 2013	8 vs. 19.8*	61.7 vs. 59.3	N/A
Figueras J, 2013	10.4 vs. 34.5*	N/A	N/A

*$p < 0.01$.

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pancreatic fistula, morbidity, and mortality. The overall analysis revealed significant differences in frequencies of intra-luminal hemorrhage ($p = 0.03$) and grade B/C pancreatic fistula ($p = 0.002$) between the two groups. However, the authors concluded that the current literature has no adequate evidence to prove that PG is superior to PJ for patients undergoing PD in postoperative complications. A standardized classification of POPF and other intra-abdominal complications may enable an objective and valid comparison between PG and PJ.

A high likelihood of anastomotic bleeding was found in patients after PG. Fibre et al. [60] reported a 12% reoperative rate due to bleeding at the pancreatic margin. In addition, PG may cause pancreatic duct obstruction and atrophy, leading to further destruction of endocrine and exocrine pancreatic function. In animal experiments, Telford et al. [61] found complete obstruction of the pancreatic duct in 90% of animals after PG. In the study comparing postoperative morphology of the remnant pancreas after PJ and PG, the main pancreatic duct tended to dilate postoperatively in the PJ group ($p = 0.0931$). On the other hand, the size of the main pancreatic duct was significantly larger postoperatively when compared with preoperatively in the PG group ($p = 0.0009$). In addition, significant postoperative atrophy of pancreas was noted in both groups ($p < 0.0001$), although these findings were more severe in the PG group ($p = 0.0018$) [62]. Lemaire et al. [63] reported reduction in pancreatic exocrine function and worsening of pancreatic atrophy after PG. In another study to evaluate pancreatic exocrine and endocrine functions after PD, PG was more frequently associated with severe steatorrhea compared with PJ (70% vs. 21.7%, $p < 0.025$), suggesting impairment of fat metabolism [64]. Thus, both PG and PJ are safe, with no significant difference in perioperative complication rates. However, the effect of PG on long term digestive physiology requires further research.

5. Isolated Roux loop pancreaticojejunostomy (IRPJ)

The rationale of creating an isolated Roux loop for drainage of pancreatic stump was initially introduced by Machado et al., in 1976 [65]. Currently, there are two refinements. One is to separate the PJ and choledochojejunostomy from gastrojejunostomy into two routes, thereby decreasing the risk of bile reflux gastritis, retrograde cholangitis, and dumping syndrome. The second and the mainstream is to separate the PJ from the choledochojejunostomy and gastrojejunostomy by an isolated Roux loop reconstruction [66]. Proponents of this technique believe that diversion of bile away from the PJ minimizes pancreatic enzyme activation and reduces the risk of pancreatic fistula. Another argument in favor of using a Roux loop in PJ relies on the belief that if a pancreatic fistula forms, it will be a pure pancreatic fistula and these fistulae cause less complication when compared with a complex pancreatic fistula in which bile activates pancreatic juice with further repercussions. In addition, an isolated Roux loop has also been used in patients undergoing PD in combination with different pancreaticenteric reconstruction such as duct to mucosa PJ [67].

In view of these expected advantages, many centers started using an isolated Roux loop of jejunum for PJ. Several cohort studies [66–71] reported a reduction in the incidence of pancreatic fistula and its related mortality, thus improving the safety of PD. However, majority of groups noticed that this technique failed to demonstrate any significant reduction of pancreatic anastomosis leakage. The data showed that complication rates; POPF rates, grade and duration of spontaneous closure; morbidity and mortality were of the same in the IRPJ group when compared to CPJ. The explanation given was healing of pancreaticoenteric anastomosis is dependent on many factors and diversion of bile is only one of them. Even activation of leaking pancreatic juice is not solely dependent on the presence of bile: intestinal juices can also activate pancreatic secretions. As IRPJ offered no advantage and the process of fashioning an isolated loop of jejunum made the entire procedure longer and more complex and increases the duration of surgery, the authors concluded that isolated IRPJ was not superior to CPJ [72]. In the nonrandomized study by Kaman et al. [73] the data also failed to show any significant difference in morbidity, POPF rates and mortality following IRPJ or conventional single-loop pancreaticojejunal reconstruction after PD. However, performance of an IRPJ entails a significant prolongation of operative time and the need for more blood transfusion. Based on limited evidence, IRPJ does not appear to offer any significant advantage than the conventional PJ.

6. Conclusion

The major methods for pancreatic and digestive tract reconstruction include conventional PJ, binding PJ, duct-to-mucosa PJ, and PG. Each of these procedures has its special features and characteristics. Large prospective studies and meta-analyses show no significant differences in postoperative complications and mortality among these reconstruction methods. Surgeons should choose whichever technique they feel comfortable with in the reconstruction of pancreatic stump after pancreaticoduodenectomy. The high rate of pancreatic fistula has been reduced with advances in surgical techniques. Assessment of long-term patency of pancreatic duct requires further clinical studies.

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Author contribution

Study conception and design: Xiao-Ping, Chen, Yong-Jun, Chen.
Acquisition of data: Eric C.H. Lai, Yong-Jun Chen.
Analysis and interpretation of data: Eric C.H. Lai, Yong-Jun Chen.
Drafting of manuscript: Yong-Jun Chen.
Critical revision: Wan-Yee Lau, Xiao-Ping Chen.

Conflicts of interest

Nothing to disclose.

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