Postoperative Complications Linked to Pancreaticoduodenectomy. An Analysis of Pancreatic Stump Management

Enrico Benzoni, Aron Zompicchiatti, Enrico Saccomano, Dario Lorenzin, Umberto Baccarani, Gianluigi Adani, Luigi Noce, Alessandro Uzzau, Carla Cedolini, Fabrizio Bresadola, Sergio Intini

Department of Surgery, University of Udine, School of Medicine, Udine, Italy.

Abstract

Aims. To analyze the role of different procedures in the management of pancreatic stump according to the incidence of postoperative morbidity derived from the data of a single center surgical population. Methods. From 1989 to 2005 we performed 76 pancreaticoduodenectomies (PD) and 26 distal pancreatectomies (DP). The surgical reconstruction after PD was as follows: 11 manual non-absorbable stitches closure of the main duct, 24 closures of the main duct with linear stapler, 17 occlusions of the main duct with neoprene glue and 24 duct-to-mucosa anastomosis. Results. In the PD group, the morbidity rate was 60%, caused by: pancreatic leakage in 48% of patients, hemorrhagic complications in 10% following surgical procedure and infectious complications in 15%. After DP we recorded: leakage in 3.9%, haemoperitoneum in 15.4% and no complications in 80.7%. The multivariate analysis showed that the in-hospital mortality was linked to the surgical procedure (PD, p=0.003) and to the following complications: pancreatic leakage (p=0.004), haemoperitoneum (p=0.00045) and infectious complications (p=0.0077). Bleeding complications, biliary anastomosis leakage and infectious complications were consequences of pancreatic leakage (p=0.025, p=0.025 and p=0.025 respectively). Conclusion. Manual non-absorbable stitch closure of the main duct and occlusion of the main duct with neoprene glue should be avoided in the reconstructive phase.

Key words

Pancreaticoduodenectomy - postoperative complication - anastomotic leak - Whipple’s procedure

Introduction

The treatment of pancreatic cancer is undertaken with two different objectives. The first is radical surgery for patients with early stage of disease, mainly stage I and partially II. In all other cases, the aim of treatment is the palliation of the distressing symptoms related to this cancer. Despite the advances made in surgical technique and perioperative care, limited progress has been made in improving the survival of patients with this disease. Five-year survival rates are 5% to 20% for patients undergoing potentially curative resection; postoperative disease recurrence occurs commonly [1-3]. Despite this, surgical resection remains the only potentially curative therapeutic option in 10% of patients for whom resection is possible [2, 3]. The most recent series from institutions specializing in the treatment of pancreatic cancer report mortality rates after surgical procedure less than 5% [1, 2]. But morbidity rates remain high: 30% to 60% [1, 2]. The majority of perioperative complications are not life threatening, though they result in increased length of hospital stay and costs, readmissions for care, and delay in adjuvant therapy. Hemorrhagic complication occurs in 5–16% of patients following pancreaticoduodenectomy (PD); pancreatic leakage is a major cause of morbidity and mortality after PD, with incidence varying between 6 and 24% and a mortality rate up to 40% [1, 4]. The variations in methods of pancreatic stump management and the volume of literature available on both main pancreatic duct and pancreaticoenteric anastomosis leak indicate the concern associated with the leakage and the continuing efforts to prevent it.

In this study we have analyzed the role of different procedures in the management of pancreatic stump after PD, according to the incidence of postoperative morbidity derived from data in a single center surgical population.

Patients and methods

From 1989 to 2005, 137 consecutive patients, who had undergone surgical interventions for pancreatic cancer, were followed up at our department. Preoperative
studies employed abdominal ultrasonography, abdominal computed tomography (CT) and endoscopic retrograde cholangiopancreatography (ERCP), with brushing for cytology. Only a few cases had undergone fine needle transduodenal biopsy during ERCP. Serum tumor markers such as carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA-19-9) were measured preoperatively. The following biological investigation were also performed preoperatively: hemoglobin, red blood cell count, white blood cell count, hematocrit, platelet count, partial thromboplastin time, prothrombin time, international normalized ratio, serum albumin, serum proteins, and liver function tests (serum bilirubin, transaminases, γ-glutamil transpeptidase, lactic dehydrogenases).

An endoscopic stenting was positioned during ERCP whenever required (obstructive jaundice) in order to reduce bilirubin serum level before surgery.

The final assessment of resectability was made during surgical intervention considering: retroperitoneal extension of the tumors, liver metastases not identified by CT, involvement or encasement of superior mesenteric artery, superior mesenteric vein or portal vein. An intraoperative pathological examination was performed on the lymph nodes of the inferior vena cava and aorta groups and of any group around the pancreatic area if they were tangible. A pathological examination of the pancreatic, duodenal and bile duct margin was made to assess the radicality of the resection. Lymph nodes were considered positive if they showed evidence of carcinoma, whether by direct extension of tumor or by metastases. Margins were considered positive if there was histological evidence of adenocarcinoma in any of the surgical margins of the resected specimen (i.e., pancreatic neck, duodenal, or bile duct margins).

We performed 76 PDs, 26 distal pancreatectomies (DP) and 35 total pancreatectomies. We excluded from the study 35 patients who had undergone total pancreatectomy, and we recorded the results of 102 patients who had underwent PD or DP.

We did not perform pylorus-preserving procedures in this series of patients. During DP, the parenchymal transection was performed with a linear stapler (either Tyco® GIA™ 60-80, or Tyco® TA™ 60-90). The surgical reconstruction after PD was as follows: 11 manual non-absorbable stitches closure of the main duct, 24 closures of the main duct with linear stapler (Tyco® TA™ 60-90), 17 occlusions of the main duct with neoprene glue and 24 duct-to-mucosa anastomosis.

We always placed drains at the time of surgery: one was placed near the suture of the transected parenchyma, if a transection with a linear stapler or a main duct closure was performed, or near the anastomosis, if a duct-to-mucosa anastomosis was performed. Another one was placed near the hepaticojejunostomy.

**Postoperative care**

Starting with the first postoperative day, we administered somatostatin or its analogs in all patients in order to inhibit pancreatic secretion.

Blood tests were performed on the 1st, 3rd, 5th and 7th days after resection. All patients underwent an X-ray chest examination on the 3rd postoperative day, and a US examination or a CT scan during the first week after resection.

When the CT scan during the 1st week after resection recorded a fluid collection around the surgical field with no accompanying symptoms, a percutaneous drainage was performed to assess the amylase content and for microbiological analysis.

Pancreatocentestic anastomotic leak was defined as: drainage of >10 mL of fluid with high amylase content (>3 times serum amylase level) for >4 days postoperatively; or percutaneous drainage of amylase-rich intra-abdominal collection/abscess; or as intraoperative demonstration of pancreaticoenteric anastomosis disruption at re-exploration. Blood transfusion was considered necessary when hemoglobin level was less than 8 g/dL and important bleeding was considered when a fall in haemoglobin >2 g/dL, haemodynamic instability and/or patient requiring >2 units of blood transfusion were recorded. Hepaticojejunostomy leak was diagnosed when a drainage of >50 mL bilious fluid after postoperative day 4 was recorded or a leak was shown by contrast radiology. Infectious complications, diagnosed when the leucocyte count was >12 000/mm³, body temperature >38.5°C and blood culture positive, were treated with antibiotics selected according to blood culture results and antibiograms.

**Statistical analysis**

Data are expressed as mean ± standard deviation and incidence is reported as percentage; χ² test was used to compare the mean values of the incidence of complications resulting between different types of “management of the duct” during PD. DP patients were assumed as a control group for comparing the postoperative complications incidence. Multivariate analysis was used to assess independent variables, which may influence survival, in-hospital death and occurrence of complications. Significant difference was defined as p<0.05. Data processing was performed using SPSS® 13.0 for Windows® Evaluation Version.

**Results**

Mean age was 62.06 ± 9.81 years. Ninety four patients had ductal adenocarcinoma; 6 of these had adenosquamous carcinoma, 24 mucinous cystadenocarcinoma, 2 serous cystadenocarcinoma. Eight patients had neuroendocrine tumors. Pathologic staging was as follows: Ia - 3.6%, Ib - 16%, Ia - 13.9%, Iib - 48.9%, III - 6.6%, IV 11%. In-hospital mortality rate was 4.37%. In the PD group, the morbidity rate was 60%, caused by: pancreatic leakage in 48% patients, haemorrhagic complication in 10% of patients following surgical procedure, and infectious complications in 15%.

Blood transfusion was requested during 50 PD procedures and the mean blood amount transfused was 1103.43 ± 978.7 cc. No differences among the PD subtype groups in the estimated blood loss were recorded.
According to the type of surgical reconstruction after PD we recorded the following complications: after manual non-absorbable stitches closure of the main duct: 27.3% no complications, 27.3% leakage, 18.1% haemoperitoneum, 27.3% infections (intra-abdominal abscess concomitant to leakage); after closure of the main duct with linear stapler: 50% no complications, 33.3% leakage, 12.5% haemoperitoneum, 4.2% infections (wound infections); after occlusion of the main duct with neoprene glue: 32.9% no complications, 55.3% leakage, 5.9% haemoperitoneum, 5.9% infections (one case of cholangitis resolved with antibiotics); after duct-to-mucosa anastomosis: 58.2% no complications, 29.2% leakage, 4.2% haemoperitoneum, 8.4% infections (intra-abdominal abscess concomitant to leakage). The statistical differences and incidence of complications resulting between different procedures of the management of pancreatic stump after PD are shown in Table 1 and Fig. 1.

Re-operation rates were: 27.2% after manual non-absorbable stitches closure of the main duct, 23.8% after closure of the main duct with linear stapler, 6% after temporary occlusion of the main duct with neoprene glue and 29.1% after duct-to-mucosa anastomosis.

A significant statistical difference, regarding re-operation rates, was found between closure of the main duct with linear stapler vs. temporary occlusion of the main duct with neoprene glue (p=0.049) and closure of the main duct with linear stapler vs. duct-to-mucosa anastomosis (p=0.003).

After DP we recorded: 80.7% no complications (a 40% rate was recorded after PD, p=n.s.), 3.9% leakage (a 48% rate was recorded after PD, p=0.03), 15.4% haemoperitoneum (a 10% rate was recorded in PD, p=n.s.).

At the multivariate analysis, in-hospital mortality was linked to the surgical procedure (PD, p=0.003) and the arising of complications: pancreatic leakage (p=0.004), haemoperitoneum (p=0.00045) and infectious complication (p=0.0077). Overall complications were linked to: age >70 yr (p=0.0139), T stage 3 (p=0.031) and N stage 2 (p=0.000001), surgical procedure (PD p=0.0018) and pancreatic residual treatment (neoprene glue closure p=0.003 and stapler closure p=0.002). Bleeding complications, biliary anastomosis leakage and infectious complications were consequences of pancreatic leakage (p=0.025, p=0.025 and p=0.025, respectively).

**Discussion**

Complications that are related to the pancreatic remnant still represent a substantial risk for death after pancreatic head resections [5-7].

Failure of a surgical anastomosis has serious consequences particularly in cases of anastomosis of the pancreas to the small bowel, because of the digestive properties of activated pancreatic secretions. An important factor in the prevention of pancreatic fistula in patients with a pancreaticojejunostomy is technical precision and gentleness in construction of the pancreatic anastomosis. Cattell [8] in 1943 advocated the necessity of a pancreaticoenteric anastomosis because of the high mortality rate when leaving the pancreatic remnant in

![Fig.1 Incidence of complications, resulting after different managements of pancreatic stump after PD; absolute values (number of patients) upon the columns. See Table 1 for statistical significance](image)

**Table 1.** Incidence of complications due to different managements of pancreatic stump after PD (χ² test) (n.s.: not significant)

<table>
<thead>
<tr>
<th>Type of management of pancreatic stump</th>
<th>Overall complications p-value</th>
<th>Leakage p-value</th>
<th>Haemoperitoneum p-value</th>
<th>Infectious disease p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manual stiches closure of the main duct (11 pts.) vs. Neoprene glue closure (17 pts.)</td>
<td>&lt;0.05</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Manual stiches closure of the main duct (11 pts.) vs. Main duct closure with stapler (24 pts.)</td>
<td>&lt;0.005</td>
<td>&lt;0.05</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Manual stiches closure of the main duct (11 pts.) vs. Duct to mucosa anastomosis (24 pts.)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>n.s.</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Neoprene glue closure (17 pts.) vs. Main duct closure with stapler (24 pts.)</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.01</td>
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<tr>
<td>Neoprene glue closure (17 pts.) vs. Duct to mucosa anastomosis (24 pts.)</td>
<td>&lt;0.005</td>
<td>&lt;0.001</td>
<td>&lt;0.05</td>
<td>n.s.</td>
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<tr>
<td>Main duct closure with stapler (24 pts.) vs. Duct to mucosa anastomosis (24 pts.)</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.01</td>
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situ, either with or without ligature of the pancreatic duct.

In the history of PD, some authors [9-11] reported that the absence of an anastomosis to the pancreatic remnant might prevent a large proportion of postoperative complications. A pancreatic fistula from the oversewn pancreatic remnant is less dangerous than one from the pancreaticojejunal anastomosis because there is no defect in the small bowel and no activation of pancreatic enzymes.

Another technique investigated has been obliteration closure of the pancreatic duct with a chemical substance, thus avoiding a pancreaticojejunal anastomosis. This method was proposed by Gebhardt et al [12], who studied the effect of occlusion of the pancreatic duct system with Ethibloc, an alcohol prolamine, in animal experiments. The pancreatic duct may also be occluded with a fibrin glue solution, Tissucol®), which was found to have a more protective effect on beta cell function than the other solutions used [13].

Di Carlo et al [14] described lower morbidity and mortality in a non-randomized trial in 50 patients using duct occlusion with neoprene glue after Whipple’s procedure, even if a side effect of permanent occlusion, that induces pancreatic atrophy and complete loss of exocrine function, was reported. Gail et al [15] found similar results with duct occlusion after Whipple’s operation in patients with chronic pancreatitis. Lorenz et al [16] noted fewer early complications in oncologic pancreatic surgery, but not in patients with chronic pancreatitis. As recently reported by Suc et al [17], who performed a prospective randomized trial on fibrin glue occlusion on the pancreatic stump, this technique did not significantly decrease the rate of intra-abdominal complications, notably pancreatic fistula, or their severity after pancreatic resection.

Recently, Bilimoria et al [18] demonstrated that the incidence of leakage is reduced significantly when the pancreatic duct is identified and directly ligated: pancreatic leak rates were 9.6 % in subgroups having duct ligation and 34.0 % in subgroup having no duct ligation (p<0.001). At multivariate analysis, failure to ligate the pancreatic duct was the only feature associated with an increased risk for pancreatic leak (p = 0.001).

In the past, a lower morbidity was recorded in the application of mechanical stapler during the parenchymal transection [19], but actually there is accordance in the usage of the stapler and its benefits, and a careful drain management is recommended to achieve a good outcome in patients with fistula [20].

The incidence of bleeding complications after PD ranges from 5 to 16%, and can occur in up to 60% in cases of pancreatic leakage [21-24]. The mortality of a bleeding complication continues to be high, ranging from 30 to 58% [23, 24]. Jaundice, hepaticojejunostomy- and pancreaticojejunostomy anastomotic leaks are associated with an increased incidence of bleeding. The consistency of pancreas, type of pancreatic reconstruction, tumor site and size and operative duration have no influence on the incidence or type of postoperative bleed. Mortality in bleeders was 34% as compared with 3% in non-bleeders [23, 24].

Based on our results, bleeding complication, biliary anastomosis leakage and infectious complications were the consequences of pancreatic leakage.

Intra-abdominal abscesses are seen in about 3-10% after PD, and a percutaneous drainage is recommended for collections larger than 5 cm. Antibiotics should be given intravenously [23, 24].

Pancreatic fistula is still an unsolved problem, as there is still no consensus on a uniform definition of fistula. The broad range drainage rates reported in the literature (2-28%) is largely a function of the definition used, and there is no evidence that a management of pancreatic stump after PD is better than others [25, 26].

We recorded a 60% rate of complications in the PD group, while only 19.3% of patients in the DP group experienced postoperative complications, and in particular only 3.9% of DP vs. 48% of PD patients (p=0.03) recorded a pancreatic fistula. We believe that a higher duct pressure and volume of pancreatic fluid into the main duct after pancreatic resection could explain the difference between PD and DP in developing complications, and the same factors could explain the different rates of complications among different approaches to the reconstructive phase. Furthermore, the blockage of the main pancreatic duct, as recorded in the occlusion with fibrin glue, even transiently, might artificially increase the secretion of pancreatic juice in the severed secondary canals or on the suture line and, consequently, both yield and support a pancreatic fistula [27].

As claimed by the literature, risk factors for pancreatic leakage comprise general factors (age, gender, jaundice, malnutrition), disease-related factors (pancreatic pathology, pancreatic texture, pancreatic duct size, pancreatic juice output) and procedure-related factors (operative time, resection type, anastomotic technique, intraoperative blood loss).

Clearly, the high morbidity and mortality rates associated with this operation underscore the magnitude and difficulty of this type of procedure. This high leak rate in the different PD groups is consistent with reports of other authors and highlights the difficulties in managing the pancreatic stump. It is interesting to note that the PD groups involving closure/ occlusion of the pancreatic duct had similar or higher leaks and overall complication rates when compared to the duct- to-mucosa anastomosis group. This is an important finding, because patients in whom a duct occlusion is performed develop severe pancreatic exocrine insufficiency that causes malabsorption.

Furthermore, as regards total pancreatectomy, which is recommended instead of pancreaticojejunal anastomosis in order not to develop postoperative complications such as leakage, it has to be taken into consideration that this procedure is associated with severe endocrine and exocrine abnormalities. Therefore a benefit could be achieved only in patients affected by insulin dependent diabetes before surgery.

In conclusion, based on our experience, we make the following recommendations: manual non-absorbable stitch closure of the main duct and occlusion of the main duct with
Postoperative complications linked to pancreaticoduodenectomy.

neoprene glue should be avoided in the reconstructive phase, and a duct-to-mucosa pancreaticojjunostomy should be preferred. We recommend pancreaticoenteric reconstruction as a standard procedure after pancreaticoduodenectomy, because all pancreatic duct occlusion techniques are associated with high rates of pancreatic fistula complicated with endocrine insufficiency.

Conflicts of interest
None to declare.

References