Arguments for an individualized closure of the pancreatic remnant after distal pancreatic resection

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Abstract

AIM: To analyze risk factors for postoperative pancreatic fistula (POPF) rate after distal pancreatic resection (DPR).

METHODS: We performed a retrospective analysis of 126 DPRs during 16 years. The primary endpoint was clinically relevant pancreatic fistula.

RESULTS: Over the years, there was an increasing rate of operations in patients with a high-risk pancreas and a significant change in operative techniques. POPF was the most prominent factor for perioperative morbidity. Significant risk factors for pancreatic fistula were high body mass index (BMI) [odds ratio (OR) = 1.2 (CI: 1.1-1.3), P = 0.001], high-risk pancreatic pathology [OR = 3.0 (CI: 1.3-7.0), P = 0.011] and direct closure of the pancreas by hand suture [OR = 2.9 (CI: 1.2-6.7), P = 0.014]. Of these, BMI and hand suture closure were independent risk factors in multivariate analysis. While hand suture closure was a risk factor in the low-risk pancreas subgroup, high BMI further increased the fistula rate for a high-risk pancreas.

CONCLUSION: We propose a risk-adapted and indication-adapted choice of the closure method for the pancreatic remnant to reduce pancreatic fistula rate.

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Key words: Distal pancreatic resection; Postoperative pancreatic fistula; Body mass index

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derived risk factors for the development of pancreatic fistula after DPR have been identified[1-22], most of them, however, cannot be influenced by the surgeon. The aim of this study was to analyze the impact of surgical technique and patient-side risk factors on pancreatic fistula rate and other measures of perioperative outcome after DPR.

**MATERIALS AND METHODS**

**Operations and standard patient care**

All patients in this study were operated in an open procedure via transverse laparotomy. The following techniques were used for closure of the pancreatic remnant: wedge-shaped incision of the cut surface, ligation of the main pancreatic duct and hand suture of the capsule (later on referred to as hand suture closure), transsection and closure with a stapling device (later on referred to as stapler closure), Roux-Y-pancreateojunostomy (later on referred to as pancreaticojunostomy) without duct-to-mucosa anastomosis and covering of the cut surface with a seromuscular omega-loop jejunal patch after main pancreatic duct ligation (later on referred to as seromuscular patch). Occasionally, a fibrin sealant (TachoSil, Nycomed Pharma GmbH, Germany) was used for suture reinforcement. Before closure of the abdomen, peritoneal drains were placed in the vicinity of the pancreatic stump or anastomosis. All patients were transferred to the intermediate or intensive care unit for surveillance for at least 1 d. Drain amylase levels were routinely measured every day for at least 3 d postoperatively and the drains were removed on day 5 when clinically appropriate. Octreotide was administered routinely if drain amylase activity was elevated (1000 U/L). Abdominal computed tomography (CT) was performed on the basis of clinical course. Suspicious intraabdominal collections were preferably treated by CT-guided interventional drainage and amylase activity was measured in every drain fluid.

**Statistical analysis**

On the basis of a prospectively maintained database at our institution, retrospective risk factor analysis was performed. The primary endpoint was pancreatic fistula of grade B or C, as defined by the International Study Group for Pancreatic Surgery[23]. Secondary endpoints included surgical morbidity and overall mortality. Tests for statistical significance were performed with the SPSS 17.0 software (SPSS Inc., Chicago, IL) with a significance level of P < 0.05. Two-sided Mann-Whitney test, two-sided Fisher's exact test, Spearman rank correlation and binary logistic regression were used for comparison of rational variables, dichotomous variables, bivariate correlation analysis and uni- and multivariate risk factor analysis, respectively.

**RESULTS**

**Patients**

Patient characteristics and histopathological findings are shown in Table 1. From February 1994 to July 2009 at our institution, 863 patients received a pancreatic resection of whom 126 patients (77 women and 49 men) received a DPR. Patient age varied between 24 and 83 years (median 61 years), with a body mass index (BMI) ranging from 16 to 41 years (median 24 years). One-fifth of patients reported alcohol abuse (mainly patients with chronic pancreatitis) and about the same percentage was diabetic, with the need of oral antidiabetic medication or insulin substitution. Chronic pancreatitis (32%) and pancreatic adenocarcinoma (29%) were the most frequent histopathological findings and about one-third showed cystic neoplasms of the pancreas or neuroendocrine tumors. In detail, cystic neoplasms were usually serious cystic adenomas (11) or mucinous cystic neoplasms (6), while intraductal papillary mucinous neoplasms (2) and solid pseudopapillary neoplasms (2) rarely occurred in the pancreatic tail.

**Operations**

Median operation time was 270 min (120-570 min). About 21% of the DPR was part of a multivisceral resection and in less than 15% the spleen was preserved. Three specialized pancreatic surgeons performed over 80% of the operations. The most frequently employed methods for closure of the pancreas were hand suture (hand suture closure 37%) and anastomosis (pancreateojunostomy 41%) (Table 1).

**Risk factor analysis for pancreatic fistula**

Univariate analysis disclosed a high BMI [odds ratio (OR) = 1.18 per unit, P = 0.001], pancreatic closure by hand suture closure (OR = 2.88, P = 0.014), cystic neoplasm of the pancreas (OR = 3.00, P = 0.029) and more generally a “high-risk pancreas” (OR = 3.00, P = 0.011) as risk factors and pancreatic ductal adenocarcinoma (OR = 0.31, P = 0.042) as a protective factor for pancreatic fistula B/C. In multivariate analysis (binary logistic regression), BMI and direct closure by hand suture were the only independent risk factors (Table 1).

In order to obtain more information about the identified risk factors, we separately analyzed two groups of patients for POPF: high-risk vs low-risk pancreas (Table 2). High-risk pancreas was defined as pathology with OR > 1 for development of pancreatic fistula in univariate analysis (Table 1). Of note, this definition is in concordance with our previous risk factor analysis of pancreatoduodenectomies[24]. As shown in Table 2, only the low-risk group showed a significantly higher pancreatic fistula rate after direct hand suture closure, while in case of a high-risk pancreas, this elevation was not significant. BMI was an additional risk factor for pancreatic fistula in high-risk patients, but had no significant effect in the low-risk group.

**Pancreatic fistula is the main source of perioperative morbidity after DPR**

Overall rate of pancreatic fistula of grade B or C was 24%. As shown in Table 3, occurrence of pancreatic fis-
Table 1  Patients and operations, univariate and multivariate analysis of risk factors for the occurrence of postoperative pancreatic fistula B/C, median (range) n (%)

| Parameter                  | No POPF (n = 96) | POPF (n = 30) | Odds ratio | P uni-variate | P multi-variate |
|----------------------------|------------------|---------------|------------|---------------|----------------|
| Patients                   |                  |               |            |               |                |
| Age (yr)                   | 61 (24-83)       | 61 (24-82)    | 61 (24-83) | 1.002         | 0.859          |
| Sex (M:F)                  | 49 (77)          | 38 (58)       | 11 (19)    | 0.884         | 0.775          |
| BMI (kg/m²)                | 24 (16-41)       | 24 (16-34)    | 27 (17-41) | 1.181         | 0.001          |
| Diabetes                   | 24 (19.0)        | 20            | 4          | 0.585         | 0.365          |
| Alcohol                    | 23 (18.3)        | 19            | 4          | 0.623         | 0.427          |
| Crea (mg/dL)               | 0.80 (0.40-1.87) | 0.80 (0.40-1.87) | 0.80 (0.40-1.40) | 0.806 | 0.827 |
| WBC (10³/μL)               | 6.9 (2.6-18.5)   | 6.9 (2.6-18.5) | 6.8 (2.2-17.7) | 0.978 | 0.759 |
| Hb (g/dL)                  | 13.2 (7.8-16.8)  | 13.1 (7.8-16.8) | 13.4 (10.7-16.6) | 1.189 | 0.174 |
| Bili (mg/dL)               | 0.6 (0.2-1.8)    | 0.6 (0.2-1.4) | 0.6 (0.2-1.8) | 0.635 | 0.545 |
| Operations                 |                  |               |            |               |                |
| Period 94-01               | 43 (34)          | 37            | 6          | 2.508         | 0.067          |
| Period 02-09               | 83 (66)          | 59            | 24         |               |                |
| OP time                    | 270 (125-570)    | 270 (125-570) | 269 (157-510) | 0.996 | 0.154 |
| DC-S                       | 18 (14.3)        | 16            | 2          | 0.357         | 0.188          |
| PJ                         | 52 (41.3)        | 43            | 9          | 0.528         | 0.154          |
| SMP                        | 9 (7.1)          | 7             | 2          | 0.908         | 0.908          |
| Splenectomy                | 109 (86.5)       | 84            | 25         | 0.714         | 0.561          |
| Multivisceral              | 26 (20.6)        | 23            | 3          | 0.353         | 0.111          |
| Histopathology             |                  |               |            |               |                |
| PDAC                       | 38 (28.6)        | 32            | 4          | 0.308         | 0.042          |
| CP                         | 40 (31.7)        | 32            | 8          | 0.727         | 0.495          |
| CNP                        | 21 (16.7)        | 12            | 9          | 3.000         | 0.029          |
| NET                        | 16 (12.7)        | 12            | 4          | 1.077         | 0.905          |
| OTH                        | 13 (10.5)        | 8             | 5          | 2.200         | 0.199          |
| High-risk                  | 50 (39.5)        | 32            | 18         | 3.000         | 0.011          |

Univariate and multivariate analysis: binary logistic regression. POPF: Postoperative pancreatic fistula (International Study Group for Pancreatic Surgery definition); CI: Confidence interval; BMI: Body mass index; DC-HS: Direct closure hand suture; DC-S: Direct closure stapler; PJ: Pancreateojejunostomy; SMP: Seromuscular patch; PDAC: Pancreatic ductal adenocarcinoma; CP: Chronic pancreatitis; CNP: Cystic neoplasia of the pancreas; NET: Neuroendocrine tumor; OTH: Other pancreatic pathology. CNPs were: 2 intraductal papillary mucinous neoplasia, 2 solid pseudopapillary neoplasia, 11 serous cystic adenoma, 6 mucinous cystic neoplasia. High-risk pancreas is defined as pathology with odds ratio > 1 i.e., other than PDAC or CP, periods of time are 1994-2001 vs 2002-2009.

Table 2  Factors influencing postoperative pancreatic fistula rate in different risk groups n (%)

| Technique          | Low-risk pancreas1 | High-risk pancreas2 |
|--------------------|--------------------|--------------------|
|                    | POPF               | CC                 | P value | POPF               | CC                 | P value |
| Hand suture        | 8/26 (30.8)        | 0.296              | 0.009   | 9/21 (42.9)        | 0.122              | 0.400   |
| PJ                 | 4/36 (11.1)        | -0.122             | 0.295   | 5/16 (31.3)        | -0.068             | 0.639   |
| stapler            | 0/11 (0)           | -0.178             | 0.124   | 2/7 (28.6)         | -0.062             | 0.667   |
| SM patch           | 0/3 (0)            | -0.088             | 0.451   | 2/6 (33.3)         | -0.021             | 0.888   |
| Risk factor        |                    |                    |         |                    |                    |         |
| BMI (kg/m²)        | 24 (17-30) vs 23 (16-32)1 | 0.178          | 0.125   | 29 (21-41) vs 25 (17-34)2 | 0.349          | 0.013   |

CC: Correlation coefficient; POPF: Postoperative pancreatic fistula (Grade B or C of the International Study Group for Pancreatic Surgery definition); BMI: Body mass index; high-risk pancreas defined as pathology with odds ratio > 1 (see Table 1); PJ: Pancreateojejunostomy; SMP: Patch seromuscular patch. 1POPF rate: 18/50 (36.0%); 2POPF rate: 12/76 (15.8%). *P* value given for correlation with occurrence of POPF (two-sided Spearman rank test).

tula B/C correlated significantly with morbidity (overall, surgical and severe morbidity), intraabdominal abscess, reoperation and longer hospital stay (Table 2). Postpancreatectomy hemorrhage and sepsis were more frequent in patients with pancreatic fistula, but constituting a nonsignificant trend. Overall mortality was below 2% and not significantly associated with pancreatic fistula. Indications for reoperation in the patients with pancreatic fistula were erosion bleeding due to pancreatic fistula (3) and intraabdominal abscess not amenable to sufficient interventional drainage (5). Reoperations in patients without pancreatic fistula were necessary because of anastomotic leakage after multivisceral resection involving the stomach (2), postoperative colonic ischemia (2), postoperative splenic ischemia (1), programmed lavage after DPR for pancreatic abscess (1), bleeding after fenestration of a liver cyst during DPR (1), abdominal abscess in absence of pancreatic fistula (2) and insufficiency of the fascia...
Table 3 Postoperative pancreatic fistula is the main factor of perioperative morbidity after distal pancreatic resection

| Parameter description for all patients (n = 126) | Groups | Correlation |
|-----------------------------------------------|--------|-------------|
| | n (%) | No POPF (n = 96) | POPF (n = 30) | Coefficient | P value |
| POPF | 30 (23.8) | 96 | 30 | 1.000 | NA |
| Overall morbidity | 76 (60.3) | 46 | 30 | 0.453 | < 0.001 |
| Surgical morbidity | 55 (43.7) | 25 | 30 | 0.635 | < 0.001 |
| Severe morbidity | 19 (15.1) | 11 | 8 | 0.181 | 0.043 |
| Inta-abdominal abscess | 17 (13.5) | 5 | 12 | 0.434 | < 0.001 |
| Septic shock | 3 (2.4) | 1 | 2 | 0.157 | 0.079 |
| PPH | 8 (6.3) | 4 | 4 | 0.160 | 0.073 |
| Reoperation | 18 (14.5) | 10 | 8 | 0.198 | 0.026 |
| Overall mortality | 2 (1.6) | 1 | 1 | 0.078 | 0.385 |
| Hospital stay (d), median (range) | 15 (8-143) | 14 (8-143) | 32 (11-108) | 0.552 | < 0.001 |

POPF: Postoperative pancreatic fistula of Grade B or C [International Study Group for Pancreatic Surgery (ISGPS) definition]; PPH: postpancreatectomy hemorrhage (ISGPS definition), severe morbidity includes complications leading to sepsis, reintubation or reoperation. Septic shock is defined as sepsis with iv catecholamin requirement. Correlations derived from two-sided Spearman’s rank correlation test. NA: Not applicable.

Table 4 Distal pancreatic resection - changing indications, demographics and operative techniques n (%)

| Parameter | 1994-2001 (n = 43) | 2002-2009 (n = 83) | P value |
|-----------|---------------------|---------------------|--------|
| Patients  |                     |                     |        |
| Age (yr, median) | 51 | 64 | 0.001 |
| BMI (kg/m², median) | 25 | 24 | 0.713 |
| Histology |                     |                     |        |
| PDAC | 8 (19) | 28 (34) | 0.097 |
| CP | 22 (51) | 18 (22) | 0.001 |
| CNP | 3 (7) | 18 (22) | 0.044 |
| NET | 5 (12) | 11 (13) | 1.000 |
| Other | 5 (12) | 8 (10) | 0.762 |
| High-risk pancreas | 13 (30) | 37 (45) | 0.129 |
| Operations |                     |                     |        |
| Multivisceral resections | 9 (21) | 17 (21) | 1.000 |
| Hand suture closure | 13 (30) | 34 (41) | 0.252 |
| Pancreateojunostomy | 30 (70) | 22 (27) | < 0.001 |
| Stapler closure | 0 (0) | 18 (22) | < 0.001 |
| Seromuscular patch | 0 (0) | 9 (11) | 0.027 |
| Perioperative parameters |                     |                     |        |
| POPF B/C | 6 (14) | 24 (29) | 0.078 |
| OHS (d) | 13 | 15 | 0.036 |

POPF: Postoperative pancreatic fistula of Grade B or C (International Study Group for Pancreatic Surgery definition); BMI: Body mass index; PDAC: Pancreatic ductal adenocarcinoma; CNP: Cystic neoplasia of the pancreas; NET: Neuroendocrine tumor; OTH: Other pancreatic pathology, high-risk pancreas defined as not PDAC or CP; OHS: Overall hospital stay, P value given for two-sided Fisher’s exact test.

Postoperative morbidity occurred due to pulmonary embolism after reoperation for pancreatic fistula with erosion bleeding (1) and shock after colon perforation due to postoperative acute myocardial infarction (1).

**DPR - changing indications, patient characteristics and operation techniques**

The number of DPRs performed per year has increased substantially. There were 43 DPR from 1994 to 2001 (n = 43) but 83 from 2002 to 2009 (Table 4). We recognized significant differences when comparing these two time periods. Median patient age increased by over 10 years (51 years vs 64 years, P = 0.001) and the indications changed. The number of DPRs performed for chronic pancreatitis strongly decreased (51% vs 22%, P = 0.001), whereas there was an increase in patients operated on for cystic neoplasms of the pancreas (7% vs 22%, P = 0.044). This translated into a higher number of operations on a “high-risk” pancreas and a tendency for a higher pancreatic fistula rate (14% vs 29%, P = 0.078), as well as a significantly longer overall hospital stay (13 d vs 15 d, P = 0.036). Regarding the operations, there were also significant changes in the preferred method of pancreatic stump closure. Pancreateojunostomy was performed less frequently while stapler closure and seromuscular patch were only performed in the last 8 years.

**DISCUSSION**

DPR was first performed successfully by Trendelenburg in 1882[25] and has since long become a standard procedure widely performed with very low mortality. However, perioperative morbidity remains substantial from the very first reported cases[25,26] to the most recent large series[1,3,5,10], the most important cause being pancreatic fistula. This is highlighted also by our present study, as we show that most of the perioperative morbidity, including severe complications and reoperations, are strongly associated with pancreatic fistula.

Several large series have identified patient-side risk factors for the development of pancreatic fistula. Among those are male gender[1,12], younger age[3], obesity[22,24], soft pancreatic texture[7] and smoking[1], whereas preoperative diabetes has been described as protective against pancreatic fistula[1]. In the present study, we could confirm BMI as the only independent patient-side factor influencing pancreatic fistula rates. It may be argued that a soft “fatty pancreas” is prone to pancreatic fistula development after DPR in the same way as shown for pancreaticoduodenectomy by us and others[8,24].

Concerning the indications for DPR, trauma to the
pancreas was identified by others to constitute a risk factor for pancreatic fistula [1,10,24]. We found that the risk of pancreatic fistula is significantly higher for cystic neoplasm of the pancreas and significantly lower for pancreatic ductal adenocarcinoma. This seems reasonable given that the pancreas is usually fibrotic in pancreatic carcinoma but healthy and soft in cystic neoplasm. In general, we could define a “high-risk pancreas” comprising of several pathologies and confirm it as a risk factor with a 3-fold elevated risk of pancreatic fistula in univariate analysis. Of note, the increased pancreatic fistula rate in the high-risk pancreas group was further exaggerated by a higher BMI.

With respect to the extent of the resection, the following risk factors for pancreatic fistula have been described: extended resection to other organs [5], extended lymphadenectomy [5], extended pancreatic resection of more than 8 cm [5,11], splenectomy [7], high blood loss [5] and long operation time [12]. Extension to multivisceral resections is relatively common in DPR, with reported rates of 15%-36% in the largest series [5,12,27]. However, only one of these series did identify multivisceral resection as a risk factor for POPF. Our study did not show an influence of operation time, splenectomy or multivisceral resection on pancreatic fistula rates. A possible reason is that extended procedures are usually not performed for the high-risk gland according to our definition, but rather in the setting of pancreatic cancer.

Our study comprised four methods of pancreatic stump closure. The method with the lowest POPF rate was stapler closure, closely followed by PJ and seromuscular patch. As a whole, these techniques performed significantly better than hand suture.

Many investigators have attempted to find the safest method with the lowest pancreatic fistula rate. By far the most frequently performed techniques are direct hand suture or stapler closure. The most recent randomized controlled trial examining the value of those two techniques is the DISPACT trial, which for the primary endpoint of operation time, splenectomy or multivisceral resection on pancreatic fistula rates. A possible reason is that extended procedures are usually not performed for the high-risk gland according to our definition, but rather in the setting of pancreatic cancer.

As our study comprised a long period of 16 years, we aimed to analyze possible bias and evolutions over time. POPF rates did not change significantly between the first and second study periods, ruling out a strong learning curve bias. On the contrary, we noted an increase in the rate of POPF. We attribute this mainly to changing indications leading to a higher percentage of high-risk glands. Especially cystic neoplasms of the pancreas are more frequently diagnosed and treated operatively. In addition, patient age increased by more than 10 years in median, accompanied by a longer hospital stay, probably due to a longer recovery period after surgery. There was a significant change in the techniques used for closure of the pancreatic remnant. While hand suture was performed at an equal frequency, PJ has been displaced by stapler closure or seromuscular patch. This reflects the attempt to simplify and improve closure techniques.

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confirmed intraoperatively on the basis of pancreatic texture, as already shown for pancreatic head resection [34].

Stapler closure needs virtually no learning curve, is safe and might therefore be the preferred technique in general. At our institution, the Ethicon Proximate Stapler® is used for stapling the pancreas. The theoretical advantage of the TA closure principle is an equal and slow adaption of the whole suture line at once. We do not use GIA stapling devices (sideways running blade and stapling) because of the risk of insufficient closure of the distal suture when tissue is pushed along the suture line. Importantly in this context, laparoscopic DPR with stapler closure has been shown to significantly reduce hospital stay [12–17] and offers the advantages of minimally invasive surgery and stapler closure. The laparoscopic approach has already been shown to reduce perioperative morbidity in DPR [18].

If stapler closure is not technically feasible, for example due to a very thick pancreas or transaction close to the pancreatic head, closure methods may be chosen depending on risk category: for a healthy and soft pancreas we propose seromuscular patch closure with main pancreatic duct ligation. This might also be done in case of a hard and fibrotic gland. However, in cases of impaired pancreatic juice outflow to the duodenum, as might be the case in chronic pancreatitis, drainage by pancreatojejunostomy may be the procedure of choice.

In summary, while serious morbidity and mortality are low after DPR, changing indications and patient demographics contribute to a constantly high pancreatic fistula rate and pose a challenge to the surgeon. Risk-adapted and indication-adapted use of closure techniques for the pancreatic stump and laparoscopic surgery are options to encounter this problem in the future.

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