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Robotic versus open pancreatoduodenectomy: a propensity score-matched analysis based on factors predictive of postoperative pancreatic fistula

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Abstract
Background Improvement in morbidity of pancreatoduodenectomy (PD) largely depends on the reduction in the incidence of clinically relevant (CR) postoperative pancreatic fistula (POPF).
Methods After internal validation of the clinical risk score (CRS) of POPF, and identification of other predictive factors for POPF, robotic (RPD), and open (OPD) PDs were stratified into risk categories and matched by propensity scores. The primary endpoint of this study was incidence of CR-POPF. Secondary endpoints were 90-day morbidity and mortality, and sample size calculation for randomized controlled trials (RCT).
Results No patient undergoing RPD was classified at negligible risk for POPF, and no CR-POPF occurred in 7 RPD at low risk. The matching process identified 48 and 11 pairs at intermediate and high risk for POPF, respectively. In the intermediate-risk group, RPD was associated with higher rates of CR-POPF (31.3% vs 12.5%) ($p = 0.0026$), with equivalent incidence of grade C POPF. In the high-risk group, CR-POPF occurred frequently, but in similar percentages, after either procedures. Starting from an unadjusted point estimate of the effect size of 1.71 (0.91–3.21), the pair-matched odds ratio for CR-POPF after RPD was 2.80 (1.01–7.78) for the intermediate-risk group, and 0.20 (0.01–4.17) for the high-risk group. Overall morbidity and mortality were equivalent in matched study groups. Sample size calculation for a non-inferiority RCT demonstrated that a total of 31,669 PDs would be required to randomize 682 patients at intermediate risk and 1852 patients at high risk.
Conclusions In patients at intermediate risk, RPD is associated with higher rates of CR-POPF. Incidence of grade C POPF is similar in RPD and OPD, making overall morbidity and mortality also equivalent. A RCT, with risk stratification for POPF, would require an enormous number of patients. Implementation of an international registry could be the next step in the assessment of RPD.

Keywords Pancreatoduodenectomy · Open pancreatoduodenectomy · Robotic pancreatoduodenectomy · Postoperative pancreatic fistula · Propensity score

For many abdominal procedures minimally invasive (MI) surgery gradually replaced open surgery or gained a well-established role [1]. For straightforward procedures, such as cholecystectomy, the benefits of laparoscopy became soon self-evident so that laparoscopy was accepted even without sound scientific evidence of superiority over open surgery [2]. For other operations, such as colorectal surgery, adoption of laparoscopy was slowed, because of both concerns on oncologic results [3] and the need for training in advanced laparoscopy [4]. In most abdominal procedures implementation of laparoscopy was confronted by the safety of open surgery [5], but could also rely on the lessons learned from open procedures, for which standardized techniques had been developed and good results had been achieved.

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MI pancreatoduodenectomy (PD) has little to share with the majority of other abdominal procedures in terms of either operative technique or postoperative morbidity. Indeed, attempts to define the ideal technique for pancreatic anastomosis in open PD have failed to demonstrate the clear superiority of one technique [6], and postoperative pancreatic fistula (POPF) continues to occur frequently leading to significant morbidity [7, 8]. MI PD is hence confronted by the unique challenge of improving the outcome of a yet imperfect open procedure. Additionally, MI PD requires extensive and meticulous dissection in deep and narrow retroperitoneal space and includes complex digestive reconstructions [9], making the inherent technical limitations of laparoscopy more evident [10].

Despite all these limitations, recent evidence shows that MI PD can be safely performed in selected patients by expert surgeons [11]. Since most of the morbidity of PD originates from POPF [7, 8], it is clear that any real improvement in the postoperative course of PD depends on the reduction of incidence and severity of POPF. All but one [12] of currently available comparisons between laparoscopic and open PD [13–17] were not based on risk stratification for development and severity of POPF, making results difficult to interpret and sometimes misleading.

Recently, Callery et al. reported the clinical risk score for pancreatic fistula (CRS-POPF). The CRS-POPF allocates a score to each of four well-established variables predictive of POPF, resulting in a cumulative 10-point risk score that predicts the development of clinically relevant POPF after PD. Risk categories for POPF are defined as follows: a score of 0 corresponds to a negligible risk, a score of 1 or 2 to a low risk, a score between 3 and 6 to an intermediate risk, and a score $\geq$7 to a high risk [18]. The CRS-POPF has been validated in open PD [19, 20], laparoscopic PD [20], and in robotic PD (RPD) [21].

We herein report a propensity score-matched comparison between RPD and open PD (OPD), having as primary endpoint the incidence of clinically relevant POPF (CR-POPF). After internal validation of CRS-POPF, our propensity score model was enhanced by the addition of all other factors that were found to anticipate the development of POPF in this series.

Robotic assistance was preferred to pure laparoscopy because of our initial encouraging experience [22], and because the enhanced surgical dexterity offered by robotic assistance [23] was thought to facilitate safe construction of pancreatic anastomosis.

Methods

This study was approved by the Institutional Review Board of the University of Pisa. A retrospective case–controlled analysis of a prospectively maintained database on all pancreatic resections was performed for all patients undergoing PD between February 1, 2007 and December 31, 2014 in whom a pancreatico-jejunostomy was used to drain the pancreatic remnant. All procedures were performed at a single institution (Division of General and Transplant Surgery, University of Pisa). Patients were excluded if individual patient research authorization was not available, and if any of the four risk factors making the CRS-POPF was missing.

Before matching RPD with OPD, the CRS-POPF was validated in the current series of PDs. Additional factors predictive of POPF, but not included in the CRS-POPF, were also defined and added to the CRS-POPF to enhance the reliability of matching. The two study groups were then matched by propensity scores.

In order to ensure a true comparison between open and robotic pancreatico-jejunostomy, and not only between OPD and RPD, only patients in whom RPD was completed without conversion to open surgery were included in the final analysis.

The primary endpoint of our study was the incidence of CR-POPF in RPD (cases), as compared with OPD (controls).

Secondary endpoints were 90-day morbidity and mortality, and sample size calculation for randomized controlled trials, having incidence of CR-POPF as the main study endpoint.

Definition of postoperative complications

All perioperative events occurring within 90 days of surgery, including hospital readmission, were considered [24, 25].

The definition provided by the International Study Group on Pancreatic Surgery (ISGPS) was used to identify POPF [26]. Grading of POPF was obtained via the online Pancreas Club Calculator [27]. Grade B and grade C POPF were considered CR-POPF. Delayed gastric emptying (DGE) [28], and post-pancreatectomy hemorrhage were also defined and graded using standardized definitions [29].

The CRS-POPF was calculated for all patients, and risk categories were then assigned as reported by Callery et al. [18]. Pancreatic texture was intraoperatively defined by the operating surgeon as either firm or soft. Because of the impossibility to palpate the gland using the robot, in RPD pancreatic texture was assessed on the specimen. Indications for PD were stratified according to pathology information. Pancreatic duct diameter was acquired intraoperatively by probing the ductal orifice with serial sized dilators until one could no longer be passed. Intraoperative blood loss was determined using the formula proposed by Gross [30] and modified by Song et al. [31].

Postoperative complications were graded according to the Clavien–Dindo classification [32]. Complications

requiring treatment under general anesthesia or intensive care (grade IIIb and higher) were defined as severe complications [33]. In patients with more than one complication, the highest grade was considered. Further, the comprehensive complication index was calculated for each patient [34].

Selection criteria for RPD

Patients were selected for RPD when generally suitable for laparoscopy, when body mass index was <35 kg/m^2, when pancreatic disease was deemed amenable to radical resection through a MI approach, and when the robotic system was timely available. Selection criteria, were slightly extended during the study period as more experience was earned [35–38], and as evidence emerged suggesting that laparoscopy could be safely adopted in selected patients with pancreatic cancer [39]. Evidence of clear margins was required for all tumor types. When, despite the initial selection, tumor adherence to portal–mesenteric vein was discovered during surgery, the operation was completed under robotic assistance, if radical resection appeared to be safely feasible [36].

Patients were informed fully about the innovative nature of RPD. Possible advantages and disadvantages of the newer operation, compared with an OPD, were presented and discussed. Patients had to sign an informed consent.

Operative techniques

The technique for RPD was previously described in detail [22, 35]. Despite all PDs, either OPD or RPD, were performed by the same surgeon (UB), RPD required several adaptations in surgical techniques:

1. In OPD all vascular pedicles were selectively ligated, while in RPD harmonic shears were used to divide the gastrocolic ligament and the mesentery of the first jejunal loop.
2. Pylorus preservation was the first choice in either procedures, but an antecolic reconstruction was preferred in OPD.
3. In OPD the neck of the pancreas was sharply divided and hemostasis was secured by individually suturing spurting bleeders. In RPD the neck of the pancreas was divided using a combination of harmonic shears and monopolar scissors. Hemostasis was achieved by either coagulating or suturing pancreatic vessels. In both OPD and RPD the duct was cut sharply.
4. Duct-to-mucosa pancreatico-jejunostomy was performed as required in either OPD or RPD. In OPD, 5-0 polypropylene sutures were used for either anastomotic layers. In RPD, 4-0 expanded polytetrafluoroethylene was used for the external layer and 5-0 polydioxanone for the duct-to-mucosa suture.
5. In OPD an omental flap was used to wrap the pancreatic anastomosis. In RPD the ligamentum teres was used to cover the stump of the gastroduodenal artery.

In both OPD and RPD, two drains (12 Fr) were positioned near the pancreatic anastomosis.

Statistics and matching strategy

Categorical variables are summarized as frequencies, percentages, and rates. Continuous variables are expressed as mean ± SD if normally distributed or as median and interquartile range (IQR) if not. Kolmogorov–Smirnov test was used to assess normality distribution.

CRS-POPF was validated in our series using Cochran–Armitage test for trend.

Chi-square test was used to evaluate the presence of an association between surgical technique (OPD and RPD) and outcome (CR-POPF). As estimate of the effect size the odds ratio (OR) was considered appropriate.

Univariate and multivariate logistic regressions were performed to identify all significant predictors of CR-POPF and to calculate the variation of the estimate effect size for each predictor, when different models were defined.

Propensity score analysis was performed to balance possible confounders between the two study groups in order to prevent any bias related to the initial selection of patients for RPD. Accordingly, before proceeding with the matched analysis, linear propensity score values were used as covariate in a logistic regression analysis for risk adjustment in the entire study population. Subsequently, linear propensity score values were used to conduct a greedy match using nearest-neighbor method and 1-to-1 ratio, with replacement, within a specific caliper width of 0.2 SD of the logit of the estimated propensity score, starting the match from cases with the largest propensity score. Post-matching covariance analysis and sensitivity analysis were then evaluated using Rosenbaum test for Wilcoxon Signed-Rank p value. The ensuing statistical models were used to define the point estimate and 95% confidence intervals (OR ± 95% CI) of the effect size and to evaluate the efficacy of RPD with respect to CR-POPF. For the statistical significance of the test of power = 80%, $p < 0.05$, two tailed significance level was used.

Sample size calculation for a non-inferiority randomized controlled trial, comparing OPD and RPD with risk stratification for POPF and having CR-POPF as the primary endpoint, was performed based on the results obtained in the current series. Sample size was estimated using the Farrington & Manning Score test at $\alpha = 0.025$,

power = 90%, and non-inferiority margin difference of 10% the actual group reference proportion.

Propensity score matching was performed using R Package, R Core Team (2014): A language and Environment for Statistical Computing, R Foundation for Statistical Computing, Vienna AT, available at http://www.r-project.org/. Propensity score analysis was carried out using the integrated development environments (IDEs) RStudio (http://rstudio.com) and Matching, MatchIt, Zelig and twang packages.

For sample size calculation, PASS 2005 software package (Hintze J 2004, NCSS and PASS, Number Cruncher Statistical System, Kaysville, Utah. www.NCSS.COM) was used.

All statistical analysis, except for propensity score matching and sample size calculation, were carried out with JMP® 9.0.1 software package for Mac, Copyright© SAS Institute Inc., SAS campus Drive, Cary, NC, USA and SPSS Statistics for Mac, Version 20.0., IBM Corp., Armonk, NY, USA.

Results

A total of 309 PDs met the inclusion criteria (OPDs = 227; RPDs = 82) (Table 1). The proportion of RPD increased from 6.5% in 2008 to 30.8% in 2014. Conversion to OPD was required in 1 patient (1.2%) because of intolerance to pneumoperitoneum.

Outcomes in the unmatched cohorts

Patients undergoing RPD had lower median age ($p = 0.0003$), lower mean BMI ($p = 0.004$), and lower mean ASA scores ($p < 0.0001$) (Table 1). Additionally, patients undergoing OPD or RPD were not evenly distributed across CRS-POPF categories and individual risk parameters (Table 2). As shown in Fig. 1, no patient undergoing RPD was classified at negligible risk for POPF (vs. 7.9% in OPD) ($p = 0.0048$), and more patients were assigned to the intermediate-risk group (70.7% vs 58.2%; $p = 0.045$). Similar proportions of patients undergoing RPD vs OPD were classified as having low-risk (8.5% vs 12.3%; $p = 0.35$) or high-risk profiles (20.7% vs 21.6%; $p = 0.87$).

Altogether, patients undergoing RPD had a higher mean CRS-POPF ($p = 0.04$) and cumulated more individual risk factors for POPF, such as soft gland texture ($p = 0.01$), unfavorable histology ($p = 0.0001$), and small duct diameter ($p = 0.005$). The only parameter in favor of RPD, with respect to the risk of developing POPF, was estimated blood loss ($p < 0.0001$).

Patients undergoing RPD had longer operative times ($p < 0.0001$), despite fewer associated vascular procedures ($p < 0.0001$), but had lower median estimated blood loss ($p < 0.0001$), lower need for blood transfusions ($p < 0.0001$), and lower number of transfused blood units ($p < 0.0001$). The use of a duct-to-mucosa technique (vs an invaginating technique) was more common in RPD ($p < 0.0001$), as it was the use of a duct stent ($p < 0.0001$). Significantly more drains were placed after OPD vs RPD ($p < 0.0001$) (Table 3).

Patients undergoing RPD and OPD developed postoperative complications in similar proportions, across all severity grades, after the two procedures, but POPF occurred more frequently after RPD ($p = 0.006$) as a result of higher occurrence of grade A ($p = 0.04$) and grade B ($p = 0.03$) POPF. The incidence of CR-POPF did not differ between the two procedures. Considering CR-POPF as primary outcome measure, the unadjusted point estimate of the effect size and its 95% confidence interval was 1.71 (0.91–3.21). The percentages of patients requiring

Table 1 Baseline characteristics of unmatched patients undergoing OPD and RPD

	OPD	RPD	Overall	*p* (test)
Number of patients (%)	227 (73.5%)	82 (6.5%)	309 (100%)	–
Median age, years (IQR)	67.4 (59.7–74.8)	61.6 (51.9–70.7)	66.2 (58–74)	0.0003 (Wilcoxon)
Gender, male (%)	125 (55.1%)	36 (43.9%)	161 (52.1%)	0.08 (Pearson)
Mean BMI, kg/m^2 (±SD)	24.8 ± 0.2	23.5 ± 0.4	24.5 ± 3.7	0.004 (*t*-test)
Prior abdominal surgery (%)	128 (56.4%)	41 (50.0%)	169 (54.7%)	0.32 (Pearson)
Mean ASA score (±SD)	2.7 ± 0.04	2.2 ± 0.07	2.6 ± 0.7	<0.0001 (*t*-test)
ASA category, *n* (%)				
I	5 (2.2%)	14 (17.1%)	19 (6.2%)	<0.0001 (Fisher)
II	73 (32.2%)	34 (41.5%)	107 (34.6%)	0.13 (Pearson)
III	141 (62.1%)	34 (41.5%)	175 (56.6%)	0.001 (Pearson)
IV	8 (3.5%)	0	8 (2.6%)	0.12 (Fisher)
V	0	0	0	–

BMI body mass index, *ASA* American Society of Anesthesiologists

Table 2 CRS-POPF and individual factors predictive of POPF in unmatched patients undergoing OPD and RPD

	OPD	RPD	Overall	*p* (test)
Mean CRS-POPF (±SD)	4.5 ± 2.4	5 ± 1.8	4.6 ± 2.3	0.04 (*t*-test)
Risk categories; *n* (%)				
Negligible risk, *n* (%)	18 (7.9%)	0	18 (5.8%)	0.005 (Fisher)
Low risk, *n* (%)	28 (12.3%)	7 (8.5%)	35 (11.3%)	0.35 (Pearson)
Intermediate risk, *n* (%)	132 (58.2%)	58 (70.7%)	190 (61.5%)	0.05 (Pearson)
High risk, *n* (%)	49 (21.6%)	17 (20.7%)	66 (21.4%)	0.87 (Pearson)
Gland texture, soft, *n* (%)	111 (48.9%)	53 (64.6%)	164 (53.1%)	0.01 (Pearson)
Pathology, ampullary, duodenal, cystic, islet cell, *n* (%)	102 (44.9%)	57 (69.5%)	159 (51.5%)	0.0001 (Pearson)
Main duct diameter, *n* (%)				
≥5 mm (%)	89 (39.2%)	18 (22.0%)	107 (34.6%)	0.004 (Pearson)
4 mm (%)	35 (15.4%)	12 (14.6%)	47 (15.2%)	0.87 (Pearson)
3 mm (%)	33 (14.5%)	5 (6.1%)	38 (12.3%)	0.05 (Fisher)
2 mm (%)	58 (25.6%)	44 (54.7%)	102 (33%)	<0.0001 (Pearson)
≤1 mm (%)	12 (5.3%)	3 (3.7%)	15 (4.9%)	0.56 (Fisher)
Main duct diameter ≤3 mm, *n* (%)	103 (45.4%)	52 (63.4%)	155 (50.2%)	0.005 (Pearson)
Estimated blood loss, *n* (%)				
≤400 mL (%)	63 (27.8%)	35 (42.7%)	98 (31.7%)	0.01 (Pearson)
401–700 mL (%)	44 (19.4%)	23 (28.1%)	67 (21.7%)	0.10 (Pearson)
701–1000 mL (%)	38 (16.7%)	14 (17.1%)	52 (16.8%)	0.94 (Pearson)
>1000 mL (%)	82 (36.1%)	10 (12.2%)	92 (29.8%)	<0.0001 (Pearson)

CRS-POPF clinical risk score for pancreatic fistula

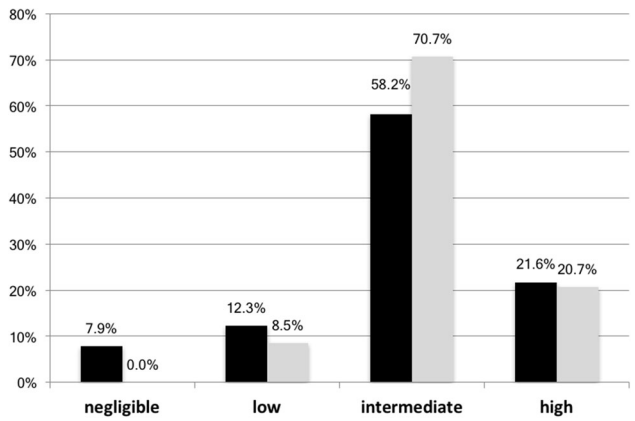

Fig. 1 Stratification of RPD (*gray columns*) and OPD (*black columns*) by CRS-POPF

interventional radiology procedures and repeat surgery were similar between the two study groups, but more patients were discharged with a drain after RPD ($p = 0.01$).

Internal validation of CRS-POPF

CR-POPF was not recorded in patients classified at negligible risk, but occurred in 1 patient at low risk (2.9%), in 34 patients at intermediate risk (17.9%), and in 18 patients at high risk (27.3%) ($p = 0.0035$). As shown in Fig. 2 the rate of CR-POPF increased along with the risk category ($p < 0.0001$). The risk of developing CR-POPF showed a similar increase with each point of the CRS-POPF ($p < 0.0001$) (Fig. 3).

Other factors predictive of POPF

Univariate logistic regression analysis showed that the development of CR-POPF could be predicted by several additional factors not included in the CRS-POPF, such as age ($p = 0.05$), BMI ($p = 0.05$), male gender ($p = 0.06$), and ASA score (0.13). These additional predictors were hence included in five different models to obtain an adjusted value of the effect size. CRS-POPF was used for the first model yielding an OR of 1.59 (0.81–3.09). Adjusting for CRS-POPF and age the OR was 1.96 (0.97–3.94). When CRS-POPF, age, and gender were considered, the OR increased to 2.07 (1.02–4.18). Adding BMI at the previous model the OR raised to 2.26 (1.10–4.64). Finally, when all variables were included into the model the effect size modification was 2.50 (1.22–5.19).

Comparison of matched cohorts (with respect to POPF)

Using the five parameters shown to predict the development of CR-POPF in the current series (CRS-POPF, age,

Table 3 Postoperative results for unmatched patients undergoing OPD and RPD

	OPD	RPD	Overall	*p* (test)
Median operative time (min) (IQR)	450 (370–520)	502.5 (450–566.3)	475 (400–540)	<0.0001 (Wilcoxon)
Pylorus preservation, *n* (%)	192 (84.6%)	76 (92.7%)	268 (86.7%)	0.06 (Pearson)
Vascular resection, *n* (%)	83 (36.6%)	7 (8.6%)	90 (29.1%)	<0.0001 (Pearson)
Vein resection	78 (34.4%)	7 (8.6%)	85 (27.5%)	<0.0001 (Pearson)
Arterial resection	2 (0.9%)	0	2 (0.7%)	1.00 (Fisher)
Arterial and Venous resection	3 (1.3%)	0	3 (1%)	0.57 (Fisher)
Median estimated blood loss (cc) (IQR)	782.4 (359.4–1244.1)	452.9 (183.6–713.9)	632.8 (311.3–1100)	<0.0001 (Wilcoxon)
Intraoperative transfusions, *n* (%)	89 (39.2%)	4 (4.9%)	93 (30.1%)	<0.0001 (Fisher)
Median number of transfused RBC units (IQR)	0 (0–1)	0 (0–0)	0 (0–1)	<0.0001 (Wilcoxon)
Type of pancreatico-jejunostomy, *n* (%)[a]				
Invaginating	136 (68.7%)	23 (36.5%)	159 (60.9%)	<0.0001 (Pearson)
Duct-to-mucosa	62 (31.3%)	40 (63.5%)	102 (39.1%)	<0.0001 (Pearson)
Duct stent, *n* (%)[b]	65 (31.3%)	45 (61.6%)	110 (39.2%)	<0.0001 (Pearson)
Median number of drains (IQR)[c]	6 (4–6)	4 (4–4)	6 (4–6)	< 0.0001 (Wilcoxon)
Median length of hospital stay (day) (IQR)				
Overall	18 (14–28)	18 (14–26)	18 (14–28)	0.93 (Wilcoxon)
Patients with CR-POPF	34 (25.8–43.8)	29 (18–37)	31 (21–41.5)	0.21 (Wilcoxon)
Postoperative complications, *n* (%)				
Grade I	14 (6.2%)	3 (3.7%)	17 (5.5%)	0.57 (Fisher)
Grade II	110 (48.5%)	44 (53.7%)	154 (49.8%)	0.42 (Pearson)
Grade IIIa	16 (7.1%)	8 (9.8%)	24 (7.8%)	0.43 (Pearson)
Grade IIIb	9 (4.0%)	6 (7.3%)	15 (4.9%)	0.23 (Pearson)
Grade IV	8 (3.5%)	0	8 (2.6%)	0.12 (Fisher)
Grade V	14 (6.2%)	3 (3.7%)	17 (5.5%)	0.57 (Fisher)
Severe postoperative complications (grade ≥IIIb), *n* (%)	31 (13.7%)	9 (11.0%)	40 (12.9%)	0.54 (Pearson)
Median comprehensive complication index (IQR)	22.6 (28.7–36.2)	22.6 (18.7–30.8)	22.6 (8.7–33.5)	0.85 (Wilcoxon)
POPF, *n* (%)	46 (20.3%)	29 (35.4%)	75 (24.3%)	0.006 (Pearson)
Grade A, *n* (%)	12 (5.3%)	10 (12.2%)	22 (7.1%)	0.04 (Pearson)
Grade B, *n* (%)	25 (11%)	17 (20.8%)	42 (13.6%)	0.03 (Pearson)
Grade C, *n* (%)	9 (4.0%)	2 (2.4%)	11 (3.6%)	0.73 (Fisher)
Clinically relevant POPF, *n* (%)	34 (15.0%)	19 (23.2%)	53 (17.2%)	0.09 (Pearson)
Percutaneous catheter drainage, *n* (%)	7 (3.1%)	6 (7.3%)	13 (4.2%)	0.10 (Pearson)
Reoperations due to POPF, *n* (%)	7 (3.1%)	2 (2.4%)	9 (2.9%)	1.00 (Fisher)
Discharged with an abdominal drainage, *n* (%)	14 (6.6%)	13 (16.5%)	27 (9.3%)	0.01 (Pearson)
Delayed gastric emptying, *n* (%)	109 (48%)	48 (58.5%)	157 (50.8%)	0.10 (Pearson)
Grade A, *n* (%)	40 (17.6%)	2 (2.4%)	42 (13.6%)	0.0002 (Fisher)
Grade B, *n* (%)	52 (22.9%)	27 (32.9%)	79 (25.6%)	0.07 (Pearson)
Grade C, *n* (%)	17 (7.5%)	19 (23.2%)	36 (11.7%)	0.0001 (Pearson)
Post-pancreatectomy hemorrhage, *n* (%)	34 (15.0%)	14 (17.1%)	48 (15.5%)	0.65 (Pearson)
Intraluminal, *n* (%)	9 (4.0%)	6 (7.3%)	15 (4.9%)	0.23 (Pearson)
Extraluminal, *n* (%)	29 (12.8%)	10 (12.2%)	39 (12.6%)	0.89 (Pearson)
Intra- and extraluminal, *n* (%)	4 (1.8%)	2 (2.4%)	6 (1.9%)	0.66 (Fisher)
Grade A, *n* (%)	1 (0.4%)	1 (1.2%)	2 (0.7%)	0.46 (Fisher)
Grade B, *n* (%)	18 (7.9%)	4 (4.9%)	22 (7.1%)	0.46 (Fisher)

Table 3 continued

	OPD	RPD	Overall	*p* (test)
Grade C, *n* (%)	14 (6.2%)	9 (11.0%)	23 (7.4%)	0.16 (Pearson)
Pathology, *n* (%)				
Pancreatic ductal adenocarcinoma	95 (41.9%)	23 (28.1%)	118 (38.2%)	0.03 (Pearson)
Ampullary adenocarcinoma	22 (9.7%)	10 (12.2%)	32 (10.4%)	0.52 (Pearson)
Malignant IPMN	24 (10.6%)	2 (2.4%)	26 (8.4%)	0.02 (Fisher)
Cholangiocarcinoma	11 (4.9%)	7 (8.5%)	18 (5.8%)	0.22 (Pearson)
Neuroendocrine tumor	14 (6.2%)	7 (8.5%)	21 (6.8%)	0.47 (Pearson)
Serous cystadenoma	6 (2.6%)	7 (8.5%)	13 (4.2%)	0.02 (Pearson)
IPMN	7 (3.1%)	6 (7.3%)	13 (4.2%)	0.10 (Pearson)
Chronic pancreatitis	11 (4.9%)	1 (1.2%)	12 (3.9%)	0.19 (Fisher)
Neuroendocrine carcinoma	6 (2.6%)	4 (4.9%)	10 (3.2%)	0.47 (Fisher)

RBC red blood cells, *IPMN* intraductal papillary mucinous neoplasm

[a] Data missing for 29 Open PD and 19 robotic PD

[b] Data missing for 19 Open PD and 9 robotic PD

[c] Data missing for 29 Open PD and 21 robotic PD

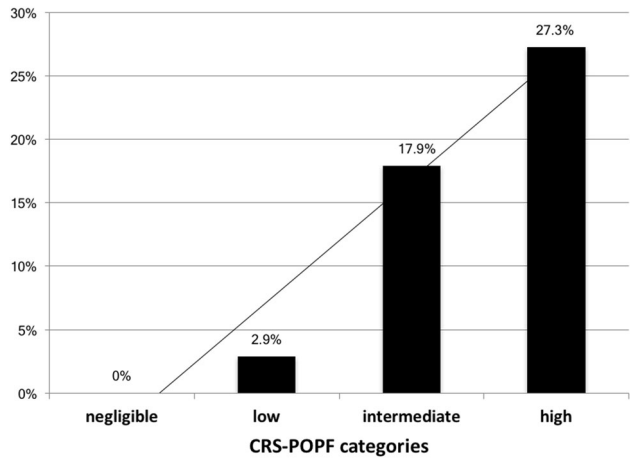

Fig. 2 Rate of CR-POPF according to CRS-POPF

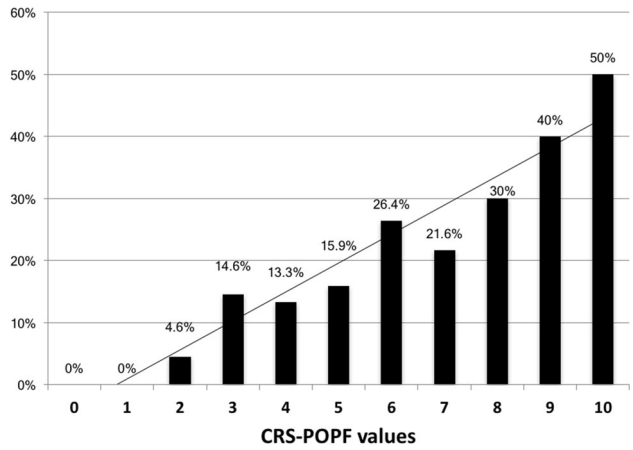

Fig. 3 Rate of CR-POPF according to each score value in the CRS-POPF

gender, BMI, and ASA score), a propensity score analysis was performed. A linear value of propensity score (PS value) was defined from propensity score analysis and was used as covariate in a logistic regression analysis to define the OR for CR-POPF in OPD and RPD. The adjusted value of the "crude" effect size varied from 1.71 (0.91–3.21) to 1.67 (0.85–4.31). The PS value was used to perform a greedy match using nearest-neighbor method and 1-to-1 ratio between RPD (cases) and OPD (controls) for patients classified at intermediate risk and at high risk in the CRS-POPF.

The matching process identified 48 and 11 pairs at intermediate and high risk for POPF, respectively. The baseline characteristics of these groups are presented in Tables 4 and 5, respectively. The two groups were comparable for all parameters. In fact, the greedy matching method produced absolute standardized mean differences lower than 0.25 for all covariates. This stringent matching method reduced sample size, but improved covariance balance.

Rosenbaum sensitivity analysis showed that the results of our propensity score matching were not sensitive to hidden biases (the lower bound of the p value overlapped the significance level within a Gamma change of 0.2).

In patients classified at intermediate risk, POPF occurred more frequently after RPD (43.8% vs 18.8%) ($p = 0.008$). CR-POPF also developed more frequently after RPD (31.3% vs 12.5%) ($p = 0.0026$). The higher incidence of CR-POPF in RPD was accounted by the more frequent occurrence of grade B POPF (27.1% vs 8.3%) ($p = 0.03$), since grade C POPF occurred in the same percentage of patients in either groups (4.2%) (Table 6).

Table 4 Baseline characteristics of matched cohorts of OPD and RPD at intermediate risk of POPF

	OPD	RPD	Overall	*p* (test)
Number of patients	48	48	96	
Median age, years (IQR)	68.8 (61–75.5)	63.4 (57.3–74)	67.3 (58.6–74.4)	0.15 (Wilcoxon)
Gender, males (%)	25 (52.1%)	26 (54.2%)	51 (53.1%)	0.84 (Pearson)
Mean body mass index, kg/m^2 (±SD)	23.5 ± 0.4	23.8 ± 0.4	23.7 ± 2.8	0.60 (*t*-test)
Mean ASA (±SD)	2.5 ± 0.09	2.4 ± 0.09	2.4 ± 0.6	0.64 (*t*-test)
Mean CRS-POPF (±SD)	4.8 ± 0.2	4.7 ± 0.2	4.8 ± 1.1	0.78 (*t*-test)

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Table 5 Baseline characteristics of matched cohorts of OPD and RPD at high risk of POPF

	OPD	RPD	Overall	*p* (test)
Number of patients	11	11	22	
Median age, years (IQR)	65.9 (60.8–72.9)	66.1 (62.8–71.1)	67.2 ± 7.2	1.00 (Wilcoxon)
Gender, males (%)	4 (36.4%)	6 (54.6%)	10 (45.5%)	0.67 (Fisher)
Mean body mass index, kg/m^2 (±SD)	24.5 ± 0.9	24.3 ± 0.9	24.4 ± 2.8	0.84 (*t*-test)
Mean ASA score (±SD)	2.8 ± 0.1	2.8 ± 0.1	2.8 ± 0.4	1.00 (*t*-test)
Mean CRS-POPF (±SD)	7.4 ± 0.2	7.7 ± 0.2	7.5 ± 0.7	0.26 (*t*-test)

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Table 6 Comparison of postoperative results of matched cohorts of OPD and RPD at intermediate risk of POPF

	OPD	RPD	Overall	*p* (test)
Median operative time (min) (IQR)	440 (371.3–493.8)	495 (450–555)	470 (412.5–540)	0.0001 (Wilcoxon)
Median length of hospital stay (days) (IQR)	16.5 (13.3–24)	18 (15–26)	18 (14–25.8)	0.38 (Wilcoxon)
Patients with complications, *n* (%)	39 (81.3%)	41 (85.4%)	80 (83.3%)	0.58 (Pearson)
Grade I	5 (10.4%)	1 (2.1%)	6 (6.3%)	0.20 (Fisher)
Grade II	27 (56.3%)	29 (60.4%)	56 (58.3%)	0.68 (Pearson)
Grade IIIa	2 (4.2%)	5 (10.4%)	7 (7.3%)	0.44 (Fisher)
Grade IIIb	1 (2.1%)	4 (8.3%)	5 (5.2%)	0.36 (Fisher)
Grade IVa	1 (2.1%)	0 (0%)	1 (1%)	1.00 (Fisher)
Grade IVb	0	0	0	–
Grade V	3 (6.3%)	2 (4.2%)	5 (5.2%)	1.00 (Fisher)
Severe postoperative complications (grade ≥IIIb), *n* (%)	5 (10.4%)	6 (12.5%)	11 (11.5%)	1.00 (Fisher)
Median cumulative complication index (IQR)	20.9 (8.7–29.6)	27.9 (20.9–30.8)	22.6 (20.9–30.8)	0.20 (Wilcoxon)
POPF, *n* (%)	9 (18.8%)	21 (43.8%)	30 (31.3%)	0.008 (Pearson)
Grade A, *n* (%)	3 (6.3%)	6 (12.5%)	9 (9.4%)	0.49 (Fisher)
Grade B, *n* (%)	4 (8.3%)	13 (27.1%)	17 (17.7%)	0.03 (Fisher)
Grade C, *n* (%)	2 (4.2%)	2 (4.2%)	4 (4.2%)	1.00 (Fisher)
Clinically relevant POPF, *n* (%)	6 (12.5%)	15 (31.3%)	21 (21.9%)	0.026 (Pearson)
Percutaneous catheter drainage, *n* (%)	1 (2.1%)	5 (10.4%)	6 (6.3%)	0.20 (Fisher)
Reoperations due to POPF, *n* (%)	2 (4.2%)	2 (4.2%)	4 (4.2%)	1.00 (Fisher)
Discharged with an abdominal drainage, *n* (%)	3 (6.7%)	12 (26.1%)	15 (16.5%)	0.02 (Fisher)
Delayed gastric emptying, *n* (%)	26 (54.2%)	31 (64.6%)	57 (59.4%)	0.30 (Pearson)
Grade A, *n* (%)	9 (18.8%)	2 (4.2%)	11 (11.5%)	0.05 (Fisher)
Grade B, *n* (%)	11 (22.9%)	17 (35.4%)	28 (29.2%)	0.18 (Pearson)
Grade C, *n* (%)	6 (12.5%)	12 (25%)	18 (18.8%)	0.12 (Pearson)
Post-pancreatectomy hemorrhage, *n* (%)	6 (12.5%)	9 (18.8%)	15 (15.6%)	0.58 (Fisher)

Table 6 continued

	OPD	RPD	Overall	*p* (test)
Intraluminal, *n* (%)	3 (6.3%)	5 (10.4%)	8 (8.3%)	0.71 (Fisher)
Extraluminal, *n* (%)	5 (10.4%)	6 (12.5%)	11 (11.5%)	1.00 (Fisher)
Intra- and extraluminal, *n* (%)	2 (4.2%)	2 (4.2%)	4 (4.2%)	1.00 (Fisher)
Grade A, *n* (%)	0	1 (2.1%)	1 (1%)	1.00 (Fisher)
Grade B, *n* (%)	2 (4.2%)	3 (6.3%)	5 (5.2%)	1.00 (Fisher)
Grade C, *n* (%)	4 (8.3%)	5 (10.4%)	9 (9.4%)	1.00 (Fisher)

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POPF occurred frequently, but in similar percentages ($p = 1.00$) in patients at high risk undergoing OPD (45.5%) and RPD (54.6%). CR-POPF developed in 36.4% of patients after OPD and in 18.2% of patients after RPD ($p = 0.64$). Grade C POPF occurred in 18.2% of patients after OPD and in none after RPD ($p = 0.47$) (Table 7).

Considering CR-POPF as the main outcome measure, starting from an unadjusted point estimate of the effect size of 1.71 (0.91–3.21), the pair-matched odds ratio was 2.80 (1.01–7.78) for the intermediate-risk group and 0.20 (0.01–4.17) for the high-risk group.

Comparison of matched cohorts (overall postoperative morbidity and mortality)

In the intermediate-risk group, RPD, was associated with longer operative times as compared to OPD, but complications were observed in similar percentages in the two groups and were scored the same severity. The only difference between the two study groups was the higher proportion of patients discharged home with a drain in place after RPD (Table 6).

In the high-risk group, no difference was noted in postoperative morbidity between the two study groups for any of the parameters listed in Table 7, including operative time.

Sample size calculation for randomized controlled trials

Based on the figures presented herein and the frequency of CR-POPF, sample size to allow a randomized controlled trial comparing RPD and OPD was calculated for both intermediate-risk and high-risk groups.

In this series RPD was possible in 32.6% of all PDs. Pancreatico-jejunostomy was performed in 94.4% of these patients, including 61.5% of the patients at intermediate risk for POPF and 21.4% of the patients at high risk for POPF. Eventually, 18.9 and 6.6% of all patients undergoing PD within the study period were eligible for RPD and were classified at intermediate or high risk for POPF, respectively.

A non-inferiority randomized controlled trial comparing RPD (no CR-POPF 72.4%) with OPD (no CR-POPF 86.4%) in patients classified at intermediate risk for POPF would require 341 pairs (α 0.025, power = 90%, non-inferiority margin of 10% corresponding to a value of 0.0864).

A non-inferiority randomized controlled trial comparing RPD (no CR-POPF 82.3%) with OPD (no CR-POPF 69.4%) in patients classified at high risk for POPF would require 926 pairs (α 0.025, power = 90%, non-inferiority margin of 10% corresponding to a value of 0.0694).

As a consequence of these estimates a non-inferiority randomized controlled trial, comparing RPD with OPD having CR-POPF as the primary endpoint, would require 682 patients at intermediate risk and 1852 at high risk. To recruit these cohorts of patients a total of 31,669 PDs would be required.

Discussion

Despite the description of different anastomotic techniques, the implementation of prophylactic measures, and the adoption of mitigation strategies [6], POPF continues to occur frequently after PD and accounts for a large proportion of postoperative complications [7, 8]. CR-POPF, in particular, needs specific care, prolongs length of stay, increases the rate of readmission, and entails additional costs [40]. Considering this background, any real improvement in the outcome of PD cannot occur without a decrease in both incidence and severity of POPF.

RPD is gaining momentum, as several pioneer surgeons have shown that the procedure was feasible [21, 35]. As for the introduction of other innovations, the surgical community soon divided between advocates [41, 42] and opponents [43, 44]. The history of MI surgery has shown that no procedure is impervious to laparoscopy, but also that good indications for open surgery remained in virtually

Table 7 Comparison of postoperative outcomes of matched cohorts of OPD and RPD at high risk of POPF

	OPD	RPD	Overall	*p* (test)
Median operative time (min) (IQR)	540 (450–600)	535 (495–720)	537.5 (468.8–601.3)	0.62 (Wilcoxon)
Median length of hospital stay (days) (IQR)	28 (21–49)	24 (16–38)	26 (18.5–40.3)	0.47 (Wilcoxon)
Patients with complications, *n* (%)	10 (90.9%)	10 (90.9%)	20 (90.9%)	1.00 (Fisher)
Grade I	0	1 (9.1%)	1 (4.6%)	1.00 (Fisher)
Grade II	6 (54.6%)	5 (45.5%)	11 (50.0%)	1.00 (Fisher)
Grade IIIa	1 (9.1%)	1 (9.1%)	2 (9.1%)	1.00 (Fisher)
Grade IIIb	2 (18.2%)	2 (18.2%)	4 (18.2%)	1.00 (Fisher)
Grade IVa	0	0	0	–
Grade IVb	0	0	0	–
Grade V	1 (9.1%)	1 (9.1%)	2 (9.1%)	1.00 (Fisher)
Severe postoperative complications (grade ≥IIIb), *n* (%)	3 (27.3%)	3 (27.3%)	6 (27.3%)	1.00 (Fisher)
Median cumulative complication index (IQR)	36.2 (22.6–56.7)	36.2 (20.9–40.6)	36.2 (22.6–43.5)	0.82 (Fisher)
POPF, *n* (%)	5 (45.5%)	6 (54.6%)	11 (50%)	1.00 (Fisher)
Grade A, *n* (%)	1 (9.1%)	4 (36.4%)	5 (22.7%)	0.31 (Fisher)
Grade B, *n* (%)	2 (18.2%)	2 (18.2%)	4 (18.2%)	1.00 (Fisher)
Grade C, *n* (%)	2 (18.2%)	0	2 (9.1%)	0.47 (Fisher)
Clinically relevant POPF, *n* (%)	4 (36.4%)	2 (18.2%)	6 (27.3%)	0.64 (Fisher)
Percutaneous catheter drainage, *n* (%)	2 (18.2%)	0	2 (9.1%)	0.48 (Fisher)
Reoperations due to POPF, *n* (%)	2 (18.2%)	0	2 (9.1%)	0.48 (Fisher)
Discharged with an abdominal drainage, *n* (%)	0 (0%)	1 (10%)	1 (5%)	1.00 (Fisher)
Delayed gastric emptying, *n* (%)	7 (63.6%)	8 (72.7%)	15 (68.2%)	1.00 (Fisher)
Grade A, *n* (%)	3 (27.3%)	0 (0%)	3 (13.6%)	0.21 (Fisher)
Grade B, *n* (%)	3 (27.3%)	4 (36.4%)	7 (31.8%)	1.00 (Fisher)
Grade C, *n* (%)	1 (9.1%)	4 (36.4%)	5 (22.7%)	0.31 (Fisher)
Post-pancreatectomy hemorrhage, *n* (%)	2 (18.2%)	4 (36.4%)	6 (27.3%)	0.64 (Fisher)
Intraluminal, *n* (%)	0	1 (9.1%)	1 (4.6%)	1.00 (Fisher)
Extraluminal, *n* (%)	2 (18.2%)	3 (27.3%)	5 (22.7%)	1.00 (Fisher)
Intra- and extraluminal, *n* (%)	0	0	0	–
Grade A, *n* (%)	0	0	0	–
Grade B, *n* (%)	1 (9.1%)	0	1 (4.6%)	1.00 (Fisher)
Grade C, *n* (%)	1 (9.1%)	4 (36.4%)	5 (22.7%)	0.31 (Fisher)

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all abdominal operations. What is currently missing is an objective assessment of RPD and OPD, based on risk stratification, so that results can be properly understood and indications for the two procedures defined.

The first important piece of information from this study is the observation that RPD differs from OPD not only because of the approach, but also because of several adaptations in the surgical technique. In RPD we performed more duct-to-mucosa pancreatico-jejunostomies, we employed duct stents more frequently, and we placed fewer drains at the end of the procedure. The higher rate of duct-to-mucosa anastomosis can be explained by the magnified view offered by the robotic system that, in combination with the use of wristed instruments, facilitates fine sutures. The use of duct stents is likely to reflect the higher rate of duct-to-mucosa anastomosis. The use of fewer drains could be explained by perceived lower invasiveness of RPD. Whatever the reasons, adaptations in surgical technique occurred and were certainly related to the MI approach, because the same surgeon performed all the procedures. Modifying the surgical technique, because of the MI approach, does not necessarily mean to do worse, or to perform at a lower level. Previous experience with laparoscopy has shown that some of these adaptations were so convenient as to be imported in open surgery. It is however worth to note that even robotic surgery does not allow the surgeon to faithfully reproduce the open procedure, as initially thought [22, 45]. Accordingly, a comparison between robotic (or laparoscopic) PD and OPD compares a "modified and minimally invasive" procedure to a "well-established and open" operation. Because of the lack of agreed standards, variations in surgical technique

among different institutions are expected to be currently greater for RPD than for OPD. A recent collaborative study, involving 55 surgeons at 15 institutions, reporting on incidence and severity of POPF after PD, demonstrated considerable variability in both risk and occurrence of CR-POPF among surgeons and institutions [46]. These variations could bias interpretation of inter-institutional data and could be particularly relevant when assessing a new procedure. Our study is based on single center and single surgeon data. Despite the fact that this study design reduced the number of procedures available for analysis, we believe that it also lessened the risk of bias coming from variations in surgical technique and postoperative management. In the hands of other surgeons, incidence and severity of POPF could have been either lower or higher than reported herein, but the differences between the two procedures should be similar.

In the unmatched cohorts RPD was associated with more risk factors for development of POPF, probably because of the initial selection of patients. This result, although quite obvious, has important implications. In the absence of risk stratification interpretation of results of MI PD could be biased, since higher rates of POPF are expected to be associated with higher rates of overall morbidity and mortality [47]. In our series, however, the higher incidence of POPF, and CR-POPF, in the unmatched cohorts was not associated with higher morbidity and mortality rates, probably because of equivalent rates of grade C POPF in the two study groups.

The main distinctive feature of this study was the stratification of patients in comparable categories based on the anticipated risk for the development of POPF. After internal validation, stratification into risk categories was performed using the CRS-POPF, with the addition of all other factors that were found to predict the occurrence of POPF in the current series. The addition of other factors, predictive of POPF, makes our study unique, since the only study published at the time of this writing that stratified patients according to the risk of POPF, employed only the CRS-POPF potentially missing other relevant prognostic factors acting as confounders [12]. The reliability of our propensity score, verified using the Rosenbaum test, improved when the additional and independent factors predictive of POPF identified in this series were added to the model. The soundness of the ensuing propensity score was extremely high. The precision of this matching process ensures that the results presented herein are very accurate and reflect the impact of surgical technique on the development of POPF while minimizing the effect of patient-specific factors. On the other hand, the number of matched pairs was proportionally reduced. Our data should therefore be interpreted carefully.

A further distinctive feature of our study was the internal validation of CRS-POPF. Considering that two of the four parameters making the CRS-POPF cannot be determined by objective methodology (i.e., assessing gland texture by palpation and estimating intraoperative blood loss), internal validation seems to be important when using CRS-POPF for risk stratification. Our internal validation of the CRS-POPF confirmed that this score predicted the occurrence and the severity of POPF. In particular, CR-POPF was not recorded in patients at negligible risk, and in 3% of the patients at low risk. Considering that CRS-POPF can be estimated at the time of surgery, this piece of information could be used to avoid drain placement and/or simplify drain management in these patients. Likewise, implementation of POPF mitigation strategies, such as administration of octreotide and/or use of duct stents, could be conveniently avoided. These measures could be particularly rewarding in a MI procedure such as RPD, as they could further enhance postoperative recovery.

Since no patient undergoing RPD was at negligible risk for POPF and no patient at low risk developed CR-POPF after RPD, propensity score matching was possible only for intermediate-risk and high-risk groups. Eventually 48 and 11 pairs were matched in the two risk groups, respectively. Although in patients at intermediate risk there were more CR-POPF, the incidence of grade C POPF was similar between the two procedures.

As expected in the high-risk group CR-POPF occurred frequently, but there was no difference between RPD and OPD. In this risk group no grade C POPF was recorded after RPD. These findings support the hypothesis that RPD is non-inferior to OPD [12]. Although the limited number of patients matched in this study does not allow us to draw a final conclusion, our results are in agreement with earlier studies [12, 14, 16, 17]. In other words, if any difference in safety favoring OPD exists, this difference is not expected to be so relevant as to preclude further development and refinement of RPD. Starting from this background the next step in the assessment of RPD should be a randomized controlled trial, but our sample size calculation showed that this study is barely feasible. On the other hand, the need to enroll an exceedingly large number of patients to run a randomized controlled trial with risk stratification for POPF, is a further, although indirect, evidence that RPD is not inferior to OPD regarding safety. An international registry, should be probably the next step in the assessment of the clinical value of RPD, until the surgical community is ready for a large multi-institutional trial.

Despite the quite high rate of POPF recorded in this series did not result in added mortality, it is clear that full exploitation of the potential benefits of RPD is largely dependent on low rates of postoperative complications.

Based on the data presented in this study we have decided to change our technique for pancreatico-jejunostomy, and we now employ the "modified Blumgart anastomosis" [48]. This technique has already been employed in both RPD [12, 21] and laparoscopic PD [49] with good results. In a retrospective study the modified Blumgart anastomosis, as compared to the Kakita pancreatico-jejunostomy, not only decreased incidence and severity of POPF but was also associated with earlier removal of surgical drains and shorter length of postoperative stay. Pancreatico-jejunostomy technique remained a prognostic factor for the development of CR-POPF also in the multivariate analysis [48]. Currently, a prospective randomized trial is ongoing, comparing the Blumgart method to the Cattell–Warren method of pancreatico-jejunostomy. Sample size calculation for this study is based on the hypothesis that the Blumgart pancreatico-jejunostomy can reduce the incidence of POPF from 20 to 10% [50].

The main limitations of this study are the retrospective nature and the limited sample size resulting in small subgroup analysis. Indeed, if on one hand, the thorough matching process ensured that the results presented herein reflect purely the effect of surgical technique on the occurence and the severity of POPF, on the other, it has produced small subgroups. Further studies still using strict matching methodology but based on larger case series are hence required.

In conclusion, RPD was associated with higher rates of POPF in patients classified at intermediate risk for POPF, but not in patients at high risk for POPF. Since the higher incidence of CR-POPF was caused by more frequent occurrence of grade B POPF, overall morbidity and mortality were equivalent in the study groups. Equivalence in surgical risk suggests that RPD may be further developed, in suitable patients and under appropriate operative conditions. Concerns on safety are further mitigated by our sample size calculation in the view of randomized controlled trials comparing RPD with OPD and having CR-POPF as the primary endpoint. The need to perform 31,669 PDs, to be able to randomize 682 patients at intermediate risk and 1852 at high risk between RPD and OPD, demonstrates that difference in safety, if present, is minimal. Probably the next step in the assessment of RPD should be the implementation of an international registry recruiting a large number of patients.

Compliance with ethical standards

Disclosures Niccolò Napoli, Emanuele Federico Kauffmann, Francesca Menonna, Francesca Costa, Sara Iacopi, Gabriella Amorese, Serena Giorgi, Angelo Baggiani, and Ugo Boggi have no conflicts of interest or financial ties to disclose.

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