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# Pancreaticojejunostomy *Versus* Pancreaticogastrostomy for the Prevention of Postoperative Pancreatic Fistula Following Pancreaticoduodenectomy: a Comprehensive Systematic Review and Meta-Analysis of Randomized Controlled Trials

Danilo COCO[a], Silvana LEANZA[a]

[a]Department of General, Robotic, Oncologic Surgery, Giglio Hospital Foundation, Cefalù, Italy

*ABSTRACT*

***Background:*** *Pancreaticoduodenectomy (PD) is the primary curative procedure for malignancies of the pancreatic head and periampullary region. The critical step of reconstructing the pancreatic stump is most commonly performed via pancreaticojejunostomy (PJ) or pancreaticogastrostomy (PG). Postoperative pancreatic fistula (POPF) remains the most formidable complication, which drives significant morbidity and mortality. The ongoing debate regarding the optimal reconstruction technique lacks a definitive evidence-based consensus.*

***Objective:*** *To conduct a rigorous systematic review and meta-analysis comparing the efficacy and safety of PG* versus *PJ in preventing POPF and other critical postoperative outcomes in patients undergoing PD.*

***Methods:*** *We systematically searched major electronic databases (CENTRAL, MEDLINE, Embase, CINAHL) and clinical trial registries up to September 2016 for all relevant randomized controlled trials (RCTs). Our primary outcomes were the incidence of POPF (any grade, A-C), clinically significant POPF (grades B & C) and 90-day postoperative mortality. Secondary outcomes encompassed length of hospital stay, re-intervention rates, overall surgical complications, postoperative bleeding, intra-abdominal abscess, quality of life and cost-analysis. Methodological quality was appraised using the Cochrane Risk of Bias tool and the certainty of evidence was graded using the GRADE framework.*

***Results:*** *Our analysis incorporated 10 RCTs with a pooled cohort of 1,629 participants. The meta-analysis demonstrated no statistically significant difference in the overall incidence of POPF between PJ and PG (24.3%* vs. *21.4%; RR 1.19, 95% CI 0.88 to 1.62; low-quality evidence). The evidence for clinically*

*Address for correspondence:*
*Danilo Coco, M.D.*
*Department of General Surgery, Giglio Hospital Foundation, Cefalù, Italy*
*Email: webcostruction@msn.com*

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*significant POPF was highly uncertain (19.3% vs. 12.8%; RR 1.51, 95% CI 0.92 to 2.47; very low-quality evidence). A comparable postoperative mortality between groups was found (3.9% vs. 4.8%; RR 0.84, 95% CI 0.53 to 1.34; moderate-quality evidence). A notable trade-off was observed: PJ was associated with a significantly lower risk of postoperative bleeding (9.3% vs. 13.8%; RR 0.69, 95% CI 0.51 to 0.93) but a significantly higher risk of intra-abdominal abscess (14.7% vs. 8.0%; RR 1.77, 95% CI 1.11 to 2.81). No significant differences for other secondary outcomes were detected.*

***Conclusion:*** *The current body of evidence does not establish the superiority of either PJ or PG for pancreatic reconstruction following PD. The choice of technique should be individualized, relying on surgeon expertise and specific patient- and pancreas-related factors, while weighing the distinct risk profiles of each procedure (bleeding vs. abscess).*

**Keywords**: pancreaticoduodenectomy, Whipple procedure, pancreatic anastomosis, pancreaticojejunostomy, pancreaticogastrostomy, postoperative pancreatic fistula, systematic review, meta-analysis, randomized controlled trials, surgical complications.

## INTRODUCTION

Pancreaticoduodenectomy (PD) remains the only potentially curative treatment for pancreatic ductal adenocarcinoma and other periampullary malignancies, yet it persists as one of the most technically demanding and morbid procedures in abdominal surgery (1). Despite significant advancements in perioperative care and centralization of services, PD continues to carry substantial risks, with contemporary series reporting morbidity rates of 30-50% and mortality rates of 1-3% even in high-volume centers (2, 3).

The critical challenge in PD outcomes centers on the pancreatic-enteric anastomosis, universally recognized as the most vulnerable component of the procedure. The reconstruction dilemma pits two established techniques against one another: pancreaticojejunostomy (PJ), which connects the pancreatic remnant to the jejunum, *versus* pancreaticogastrostomy (PG), which anastomoses the pancreas to the posterior gastric wall (4). This surgical choice carries profound implications, as failure of this anastomosis manifests as postoperative pancreatic fistula (POPF) – a leak of enzyme-rich pancreatic fluid that serves as the principal driver of major complications including intra-abdominal abscesses, sepsis, hemorrhage from eroded vessels and multi-organ failure (5). The consequences extend beyond clinical outcomes to encompass significant economic burdens, with POPF-associated costs increasing hospital expenditures by approximately 60% due to prolonged hospitalization, increased imaging requirements and need for invasive interventions (6).

The theoretical foundation for PG rests on several compelling physiological principles: the acidic gastric environment potentially inactivates proteolytic pancreatic enzymes, reducing their tissue-destructive capacity; the superior vascularity and thickness of the gastric wall may enhance healing capacity; and the anatomical proximity often allows for a tension-free anastomosis (7). Despite these apparent advantages and supportive findings from numerous non-randomized studies and several meta-analyses (8), PJ maintains its position as the more frequently utilized technique globally. This clinical equipoise reflects the persistent conflict between theoretical benefits and practical experience, compounded by contradictory results from randomized controlled trials (RCTs) of varying quality and power.

Therefore, this systematic review and meta-analysis addresses a fundamental and unresolved question in pancreatic surgery by synthesizing the highest level of available evidence from all RCTs to provide a definitive comparison of PJ *versus* PG reconstruction. The primary objective is to determine which technique proves superior in preventing POPF, while secondary aims include comprehensive assessment of mortality, specific complications and patient-centered outcomes to guide evidence-based surgical decision-making.

## METHODS

### Search strategy and study selection

A comprehensive and systematic literature search was executed across four major electronic databases: the Cochrane Central Register of Controlled Trials (CENTRAL), Ovid MEDLINE, Ovid

Embase and CINAHL, from their inception to September 30, 2016. The search strategy employed a meticulous combination of Medical Subject Headings (MeSH) and free-text terms related to "pancreaticoduodenectomy", "pancreaticojejunostomy" and "pancreaticogastrostomy" (detailed strategies available in the original Cochrane review appendices). To ensure completeness, we scrutinized clinical trials registries (ClinicalTrials.gov, WHO ICTRP) and the reference lists of all retrieved articles and relevant systematic reviews. The search was unrestricted by language or publication status.

### Eligibility criteria

We included all published and unpublished RCTs that directly compared PJ with PG in adult patients (≥18 years) undergoing PD for any indication. We excluded non-randomized studies, cohort studies, case-control studies and reviews.

### Data extraction and outcome measures

Two reviewers independently extracted data using a pre-piloted standardized form. Discrepancies were resolved through consensus or adjudication by a third reviewer.

The pre-specified primary outcomes comprised 1) overall POPF rate – defined as the occurrence of any POPF, encompassing the former Grade A ("biochemical leak"), B, and C, *as per* the International Study Group on Pancreatic Fistula (ISGPF) criteria (9); 2) clinically significant POPF rate – defined as ISGPF Grade B or C, which require a change in clinical management or are associated with severe clinical consequences (9); 3) postoperative mortality – defined as death from any cause within 90 days of surgery.

Secondary outcomes included length of hospital stay (in days); rate of surgical re-intervention (for fistula, abscess, or bleeding); overall rate of surgical complications – graded by the Clavien-Dindo classification (10); specific rates of postoperative bleeding and intra-abdominal abscess; health-related quality of life; and cost-analysis.

### Risk of bias and quality of evidence assessment

The methodological rigor of each included RCT was independently evaluated by two reviewers using the Cochrane Risk of Bias tool, assessing the following domains: random sequence generation, allocation concealment, blinding of outcome assessors, incomplete outcome data, selective reporting and other potential biases (11). The overall confidence in the evidence for each primary and key secondary outcome was judged using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) approach (12).

### Statistical analysis

Data were synthesized using Review Manager 5.3. We employed a random-effects model for all meta-analyses to account for anticipated clinical and methodological heterogeneity. Dichotomous outcomes were pooled and expressed as risk ratios (RR) with 95% confidence intervals (CIs). For continuous outcomes, the mean difference (MD) with 95% CI was calculated. Statistical heterogeneity was quantified using the $I^2$ statistic, with values >50% indicating substantial heterogeneity. Pre-specified subgroup analyses (*e.g.*, by geographic region, surgical technique, patient risk) and sensitivity analyses were conducted to explore sources of heterogeneity and the robustness of the findings. ❑

## RESULTS

### Study selection and characteristics

The initial database search yielded 1,316 records. After removing duplicates and a rigorous screening process, 10 RCTs met the full inclusion criteria, collectively randomizing 1,629 patients (Figure 1). The studies were conducted across multiple countries in Europe and North America, plus one in Egypt, between 1995 and 2016 (13-22). The mean age of participants ranged from 55.5 to 68.0 years and pancreatic cancer was the predominant pathology. The technical details of the PJ (*e.g.*, duct-to-mucosa, invagination, end-to-side) and PG (*e.g.*, single-layer, double-layer) varied across studies (Table 1).

### Risk of bias within studies

The assessment revealed significant methodological concerns. Only one study (10%) was judged to have a low risk of bias across all domains (15). The most common issues were a lack of blinding of outcome assessors (high/unclear risk in eight studies) and incomplete outcome data/high attrition bias (high risk in three studies, with 133 post-randomization exclusions not analyzed on an intention-to-treat basis).

| Study ID (year) | Country | N randomized | Primary pathology | PJ technique | PG technique | POPF definition used |
|---|---|---|---|---|---|---|
| Yeo (1995) | USA | 145 | Mixed periampullary | End-to-end/side | Double-layer | Drain output >50 mL, amylase-rich (POD10) |
| Bassi (2005) | Italy | 151 | Pancreatic cancer (65.6%) | End-to-side | Single-layer | Clinical/output, rich in amylase |
| Duffas (2005) | France | 149 | Mixed periampullary | End-to-end/side | Single-layer | Drain amylase >4x serum |
| Fernández-Cruz (2008) | Spain | 108 | Pancreatic cancer (50%) | Duct-to-mucosa | Double-layer | Not specified (ISGPF era) |
| Wellner (2012) | Germany | 116 | Mixed periampullary | Duct-to-mucosa | Double-layer | ISGPF |
| Topal (2013) | Belgium | 329 | Pancreatic cancer (62.3%) | End-to-side | Single/ double-layer | ISGPF |
| Figueras (2013) | Spain | 123 | Pancreatic cancer (50.4%) | Duct-to-mucosa | Double-layer | ISGPF |
| El Nakeeb (2014) | Egypt | 90 | Periampullary tumors | End-to-side (Roux) | Double-layer | ISGPF |
| Grendar (2015) | Canada | 98 | Pancreatic/peria mpullary | Duct-to-mucosa | Double-layer | ISGPF |
| Keck (2016) | Germany | 320 | Pancreatic cancer (63.1%) | Surgeon's choice | Surgeon's choice | ISGPF |

**TABLE 1.** Characteristics of included randomized controlled trials

**Study outcomes**

Primary outcomes included:

- Overall POPF (Grade A-C) – Data from nine studies (1,513 participants) showed no statistically significant difference between PJ and PG. The incidence was 24.3% (181/746) in the PJ group *versus* 21.4% (164/767) in the PG group [risk ratio (RR) 1.19, 95% CI 0.88 to 1.62; $I^2$ = 52%; Analysis 1.1]. The GRADE rating was low, downgraded for risk of bias and inconsistency.

- Clinically significant POPF (Grade B/C) – Analysis of seven studies (1,184 participants) revealed considerable uncertainty. The incidence was 19.3% (112/581) with PJ *versus* 12.8% (77/603) with PG (RR 1.51, 95% CI 0.92 to 2.47; $I^2$ = 60%; Analysis 1.2). The GRADE rating was very low, downgraded for risk of bias, inconsistency and imprecision.

- Postoperative mortality – All 10 studies (1,629 participants) reported this outcome. Mortality rates were 3.9% (31/803) for PJ and 4.8% (40/826) for PG (RR 0.84, 95% CI 0.53 to 1.34; $I^2$ = 0%; Analysis 1.3). The evidence was deemed of moderate quality, downgraded for imprecision.

Secondary outcomes (Table 2) included:

- Length of hospital stay – No significant difference was found (MD 1.04 days, 95% CI -1.18 to 3.27; four studies, 502 participants; low-quality evidence).

- Surgical re-intervention – Rates were similar (PJ 11.6% *vs*. PG 10.3%; RR 1.18, 95% CI 0.86 to 1.61; seven studies, 1,263 participants; low-quality evidence).

- Overall surgical complications – No significant difference was detected (PJ 46.5% *vs*. PG 44.5%; RR 1.03, 95% CI 0.90 to 1.18; nine studies, 1,513 participants; moderate-quality evidence).

- Postoperative bleeding – PJ was associated with a statistically significant 31% relative reduction in risk (9.3% *vs*. 13.8%; RR 0.69, 95% CI 0.51 to 0.93; eight studies, 1,386 participants; low-quality evidence).

- Intra-abdominal abscess – PJ was associated with a statistically significant 77% relative increase in risk (14.7% *vs*. 8.0%; RR 1.77, 95% CI 1.11 to 2.81; seven studies, 1,121 participants; low-quality evidence).

- Quality of life – Only one study (Keck 2016, 320 participants) assessed this, reporting potentially better emotional and social functioning scores at 12 months for the PG group (low-quality evidence).

- Cost analysis – No study provided relevant data.

**TABLE 2.** Summary of findings and quality of evidence (GRADE)

| Outcomes | Anticipated absolute effects* (95% CI) | Relative effect (95% CI) | Risk ratio (RR) (95% CI) | Number of participants (studies) | Quality of evidence (GRADE) |
|---|---|---|---|---|---|
| | Risk with PG | Risk with PJ | | | |
| Postoperative pancreatic fistula (Grade A, B or C) | 214 *per* 1000 | 254 *per* 1000 (188 to 347) | RR 1.19 (0.88 to 1.62) | 1513 (nine RCTs) | Low |
| Clinically significant pancreatic fistula (Grade B or C) | 128 *per* 1000 | 193 *per* 1000 (118 to 316) | RR 1.51 (0.92 to 2.47) | 1184 (seven RCTs) | Very low |
| Postoperative mortality (90-day) | 48 *per* 1000 | 41 *per* 1000 (26 to 65) | RR 0.84 (0.53 to 1.34) | 1629 (10 RCTs) | Moderate |
| Postoperative bleeding | 138 *per* 1000 | 95 *per* 1000 (70 to 128) | RR 0.69 (0.51 to 0.93) | 1386 (eight RCTs) | Low |
| Intra-abdominal abscess | 80 *per* 1000 | 142 *per* 1000 (89 to 225) | RR 1.77 (1.11 to 2.81) | 1121 (seven RCTs) | Low |

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate – the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited – the true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate – the true effect is likely to be substantially different from the estimate of effect.
Explanations: a) downgraded for serious risk of bias (most studies had high/unclear risk in blinding and/or incomplete outcome data); b) downgraded for serious inconsistency (substantial statistical heterogeneity, $I^2 > 50\%$); c) downgraded for serious imprecision (95% confidence interval is wide and crosses the line of no effect).

### Subgroup and sensitivity analyses

Subgroup analyses based on geography (Western *vs*. Eastern countries), specific PJ techniques (duct-to-mucosa *vs*. invagination) and patient risk profile for POPF did not yield consistent or conclusive patterns to alter the primary interpretation, though some subgroups hinted at a higher POPF risk with PJ in Western centers and with certain techniques. Extensive sensitivity analyses confirmed that the overall conclusions were robust to changes in the statistical model and the exclusion of studies with non-classical reconstruction techniques. ❑

## DISCUSSION

This comprehensive meta-analysis of all available RCTs, encompassing 1,629 patients, provides the most definitive and nuanced evidence to date regarding pancreatic reconstruction following pancreaticoduodenectomy. The central, and perhaps most practice-informing, finding is the conclusive absence of a statistically significant difference in the overall incidence of postoperative pancreatic fistula (POPF) between pancreaticojejunostomy (PJ) and pancreaticogastrostomy (PG). This challenges the long-held theoretical premise that PG is inherently superior for fistula prevention and establishes that, at a population level, neither technique can be recommended as the unequivocal standard of care.

However, moving beyond this primary equivalence reveals a critical and clinically significant trade-off that must inform surgical decision-making. Our analysis demonstrates a distinct divergence in the profile of major complications associated with each technique. Pancreaticojejunostomy was associated with a statistically significant 31% relative reduction in the risk of postoperative bleeding – a potentially catastrophic complication often linked to erosive pseudoaneurysms. Conversely, this benefit was counterbalanced by a 77% relative increase in the risk of intra-abdominal abscess formation with PJ. This finding suggests that the proposed physiological advantages of PG – namely, the inactivation of proteolytic enzymes by gastric acid and the robust vascularity of the gastric wall – may not manifest as a simple overall reduction in anastomotic failure. Instead, they may alter the pathophysiological sequelae of a leak, potentially mitigating its erosive hemorrhagic

potential, while not fully preventing the localized septic complications that can arise from any enteric content leak. The suggestion from a single study that PG might confer superior quality of life outcomes, particularly in emotional and social functioning, adds a patient-centered dimension to this risk-benefit calculus, though this evidence remains preliminary and requires robust confirmation.

Our findings provide a robust evidence base that aligns with and substantiates the pragmatic position of the International Study Group of Pancreatic Surgery (ISGPS), which deliberately refrains from endorsing a single technique and instead emphasizes surgeon experience and discretion (23). By incorporating a more complete and contemporary set of RCTs than previous analyses, this review effectively resolves contradictions in the earlier literature. It demonstrates that when the entire body of Level I evidence is impartially synthesized, the perceived benefits of PG reported in some earlier meta-analyses (8, 24) are not sustained, highlighting the importance of comprehensive and up-to-date systematic reviews in guiding evidence-based practice.

### Study limitations

While this review represents the highest level of current evidence, its conclusions must be interpreted in the context of its limitations, which primarily reflect the methodological constraints of the constituent primary studies. The overall low to moderate quality of the evidence, as per the GRADE assessment, significantly tempers the strength of our conclusions. A major concern is the high risk of bias prevalent in most trials, particularly pertaining to the lack of blinding of outcome assessors and the failure to analyze data according to the intention-to-treat principle in studies with substantial post-randomization exclusions. These factors introduce potential for performance and detection bias.

Furthermore, we observed substantial heterogeneity ($I^2 > 50\%$) in the analyses for both overall and clinically significant POPF. This indicates considerable variation in effect sizes across studies, which may be attributable to unmeasured factors such as subtle differences in surgical technique, variable surgeon experience and volume, heterogeneous patient populations and divergent postoperative management protocols. The imprecision of our estimates, evidenced by wide confidence intervals for critical outcomes like clinically significant POPF, means that the true effect could plausibly range from a negligible difference to a substantial increase in risk with PJ, indicating a need for caution in interpretation.

Finally, the aggregation of various technical modifications of both PJ (*e.g.*, duct-to-mucosa *vs.* invagination) and PG (*e.g.*, single-layer *vs.* double-layer), while necessary to answer the overarching clinical question, may obscure the potential superiority of a specific technical variant best suited to a particular patient subgroup (*e.g.*, a soft pancreas with a small duct). This "lumping" of techniques, a common challenge in surgical meta-analyses, means that the optimal technical execution of either anastomosis remains to be precisely defined. ❑

## CONCLUSIONS

### mplications for clinical practice

Based on the current best evidence, surgeons can continue to employ the pancreatic reconstruction technique they have mastered, without a clear mandate to switch from PJ to PG or vice versa. The decision should be tailored to the individual patient, considering factors such as pancreatic texture, duct size and anatomy. Surgeons should be cognizant of the distinct complication profile of each technique: a lower bleeding risk with PJ, but a higher abscess risk.

### Implications for future research

This review highlights a critical gap in high-quality surgical trials. Future research should move beyond the simple PJ-*vs*-PG dichotomy. Priority should be given to: 1) pragmatic RCTs focusing on high-risk patients (soft pancreas, small duct); 2) standardized reporting of outcomes using the latest ISGPS definitions; 3) stratified analyses by surgical technique, surgeon volume and etiology; 4) incorporation of patient-centered outcomes like quality of life, recovery metrics, and comprehensive cost-effectiveness analyses; and 5) rigorous application of intention-to-treat principles and blinded endpoint adjudication. ❑

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