**Management of the Pancreatic Transection Plane After Left (Distal) Pancreatectomy: Expert consensus guidelines by**

**the International Study Group of Pancreatic Surgery (ISGPS)**

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**SUMMARY**

Clinically relevant questions were derived from a series of discussions and literature review in order to evaluate the various surgical techniques and outcomes used to manage the pancreatic transection plane after left (distal) pancreatectomy by members of the International Study Group of Pancreatic Surgery. Six domains were identified where there was strong consensus that will determine a change in priority setting for clinical practice whilst a lower level agreement in eight domains will require further research to indicate future key areas of practice for managing the transection plane after left pancreatectomy.

**ABSTRACT**

**Background:** The aim was to evaluate the various surgical techniques and outcomes used to manage the pancreatic transection plane (or stump) after left (distal) pancreatectomy (LP) and to develop expert consensus guidelines.

**Methods:** Evidence based clinically relevant questions were discussed, then circulated amongst members of the International Study Group of Pancreatic Surgery. Following agreement of the questions and statements, voting in a nine-point Likert scale was used to gauge the level of objective support for each.

**Results:** Studies using the ISGPS definition of post-operative pancreatic fistula (POPF) including 16 randomized trials were reviewed, to generate a series of statements set into 14 domains. There was strong consensus that there was no difference in the POPF rate after LP between the handsewn and stapler techniques; a stapling technique could not be used in all cases of LP; the use of an energy-based tissue sealant, or a chemical sealant device or combinations of these did not impact on the POPF rate; there was no difference in the POPF rate between the open, laparoscopic or robotic approaches; and there are one or more clinically significant patient-related risk factors associated with the POPF rate. There was weak or conditional agreement on the use of prophylactic somatostatin analogues, stents, stump closure, stump anastomosis, and the role of abdominal drains.

**Conclusions:** Areas of strong consensus will require a change in clinical practice and priority setting. Eight domains with lower agreement will require novel approaches and large multicenter studies to determine future key areas of practice.

**Key Words**

Left pancreatectomy, distal pancreatectomy, postoperative pancreatic fistula, transection plane, stump, prophylaxis, risk factor, laparoscopic surgery, robotic surgery, complications.

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**BACKGROUND**

Post-operative pancreatic fistula (POPF) following left (or so called distal) pancreatectomy occurs in 20-35% of cases (1). It can be a major cause of peri-operative morbidity with prolonged hospital stay, and increased healthcare costs (1-3). The ISGPS has developed and validated a universally applicable definition for POPF (2). In the present expert consensus guideline based on systematic reviews according to the GRADE approach, we provide the current evidence from the literature with critical appraisal for various clinical issues related to the management of the pancreatic transection plane and prediction/prevention of POPF after left pancreatectomy (3).

**METHODS**

A set of proposals to develop ISGPS guidelines for the management of the pancreatic transection plane following a left (distal) pancreatectomy was initially suggested by a working group of surgeons from the Nanjing Pancreas Center, Nanjing China led by the Director, Professor Yi Miao, in July 2018. This was considered and supported by the ISGPS Core Committee (C. Bassi, M. Büchler, C. Dervenis, and J. Neoptolemos). The working group was asked to undertake an extensive literature review with instructions how to evaluate the level of evidence according to the GRADE (Grading of Recommendations Assessment, Development, and Evaluation).

An extensive literature search was performed in Pubmed/Medline by October 18, 2018. Medical subject headings (MeSH) were used wherever possible. Search strategy used in the current study was as following: “(left pancreatectomy OR distal pancreatectomy OR pancreato splenectomy OR spleno pancreatectomy) AND (pancreatic fistula [MeSH] OR postoperative complications [MeSH] OR stump closure OR handsewn OR surgical stapler [MeSH] OR pancreatic anastomosis OR pancreaticojejunostomy [MeSH] OR pancreaticogastrostomy OR electrocoagulation [MeSH] OR radiofrequency ablation OR tissuelink OR ultrasonic activated device OR fibrin sealant pancreatic ducts [MeSH] OR sphincter of oddi [MeSH] OR stents [MeSH] OR patch OR coverage OR risk factors [MeSH] OR drainage [MeSH] OR somatostatin [MeSH] OR octreotide [MeSH] OR laparoscopy [MeSH] OR laparoscopic surgery OR robotic surgical procedures [MeSH] OR robotic surgery OR minimally invasive surgical procedures [MeSH])”. Additionally, reference lists were searched by hand for relevant literature.

Studies were considered for inclusion and evaluation if they meet the following inclusion/exclusion criteria. Inclusion criteria: 1) clinical study, 2) study only focused on or mainly focused on left pancreatectomy, and 3) study specific for the management of the pancreatic transection plane. Exclusion criteria: 1) non-English, 2) publication date earlier than 2005/01/01, 3) not using ISGPS definition or its 2016 updates for reporting POPF, 4) papers of reviews, comments, response to comments, study protocols, and case reports.

A series of key questions were determined with a list of statements attached to each question for discussion prior to agreement by the ISGPS of both the questions and agreement. In August and October 2018, a preliminary paper with the literature search， with the proposed key questions and statements was sent to all members of the ISGPS. Additional literature comments and modifications were then introduced into several iterations of a daft paper. The most up to date version of the proposals were discussed at a meeting of members of the ISGPS at the Nanjing Pancreas Forum, Nanjing, China 11 October 2018 (see Acknowledgements). The quality of evidence, was assessed using the GRADE approach, as adapted for “UpToDate” (http://www.uptodate.com/home/grading-tutorial). Quality assessment of evidence was graded as ‘high’ if there was (very) low probability of further research substantially changing the conclusions, ‘moderate’ if further research might completely change the conclusions, and ‘low’ if further research was likely to completely change the conclusions. The strengths of the recommendation were graded as ‘strong’ if it was very certain that benefits outweigh risks and burdens, ‘weak’ if risks and burdens appear to be finely balanced, or when benefits, risks, and burdens are closely balanced or uncertain, or ‘conditional’ if it was in between strong and weak recommendation.

The subsequent iteration was sent to all ISGPS members for further comments. Following the final agreement of the questions and statements, the ISGPS members were asked to vote individually for each question. To gauge the level of objective support from the international expert panel, voting was used in a nine-point Likert scale was used to measure the level of agreement of the international expert panel members with the recommendations and their GRADE score. For agreement the voting results were classified using the percentage of votes that were 7 or above (the alpha-score) as either strong (α-score≥ 80%), conditional (α-score -score ≥ 65%), or weak (α-score < 65%). The results were reviewed by all ISGPS members to ensure the general relevance and applicability of the conclusions. Some of the statements were not strict guidelines, but rather consensus of varying degrees as measured by the Likert method to enable a uniform nomenclature. The final version of the manuscript was approved by all of the co-authors.

**RESULTS**

Fourteen domains were identified, each with agreed wording for each set of questions question and statements prior to anonymized voting.

**Question 1:** *Does either the handsewn technique or the stapler technique for stump closure after left pancreatectomy reduce the POPF rate compared to each other or other methods?*

**Statement 1-1:** There is no difference in the POPF rate after left pancreatectomy between the handsewn and stapler techniques.

***Quality assessment: high; Recommendation: strong; Agreement: strong* (α=94.1%).**

**Statement 1-2:** Specifically, the handsewn fish-mouth technique does not decrease the POPF rate after left pancreatectomy compared to other techniques.

***Quality assessment: moderate; Recommendation: strong; Agreement: conditional* (α=79.4%).**

**Comment**

Handsewn closure of the remnant stump after left pancreatectomy can be accomplished in various ways including the use of a “U” shape suture, interrupted mattress suture or running suture (4-6). Utilization of a stapler for transection of the pancreas is now the most popular method (3, 7, 8). In a multicentric study of 388 patients from Japan, the stapler technique had significantly fewer clinically relevant POPFs (CR-POPF) in comparison with the non-stapler technique (21.0% vs. 50.6%, respectively) (9). In the FIABLE randomized trial, there were significantly more CR-POPFs after hand-sewn (32.3%) than with mechanical closure (19.8%) (10). In a multinational study of 2026 patients from 10 centers, use of the stapler technique also had significantly fewer CR-POPFs (12.7%) compared to handsewn (19.1%) and energy sealing device (24.2%) techniques (11).

In contrast a number of large series have shown that the hand-sewn technique actually had lower POPF rates in comparison with the stapler technique (12-14). Other studies have found no difference in the POPF incidence between these two techniques (4, 15-24). The DISPACT multicentric randomized controlled trial of 352 patients in 21 European centers (2006-2009) showed that 56 (32%) of 177 patients with a stapled closure developed a POPF compared to 49 (28%) of 175 patients who had suture closure, as well as there being no significant differences with regards to intra-abdominal fluid collections or abscess, (in both arms 19%) and 90-day mortality (in both arms 3%) rates (22).

Some surgeons favor the fish mouth technique as thismay facilitate the closure of anterior and posterior surfaces of the stump (4, 6). In the study by Ferrone et al from MGH, Boston, pancreatic stump fish-mouth suture closure resulted in a POPF in 67 (30%) out of 227 patients (4).There is no evidence of superiority of the fish-mouth over other transection plane closure techniques, and it might be associated with an increased risk of bleeding (4, 6, 13, 25).

Another technical question was whether surgeons should use gradual compression technique during closing of the stapler (with or without a previous clamping of the gland with an non-crushing intestinal clamp), to avoid crushing of the pancreas parenchyma (7, 26, 27). Prolonged peri-firing compression may be associated with a lower CR-POPF rate after stapling (28, 29). Other approaches include the use of different types of stapler, thicker staplers (4.1mm and 4.5mm), and staplers with multiple rows, but none have a demonstrable advantage (26, 30, 31).

**Question 2:** *Does the reinforced stapler technique reduce the POPF rate after left pancreatectomy when compared with the regular stapler.*

**Statement 2-1:** The reinforced stapler technique reduces the CR-POPF rate after left pancreatectomy in comparison with the regular stapler technique.

***Quality assessment: moderate; Recommendation: conditional; Agreement: weak* (α=61.8%).**

**Comment**

The materials used in the reinforced stapler technique include collagen or synthetic copolymer material based products, with wide CR-POPF rates reported ranging from zero to 33% (4, 11, 30, 32-37). In the only randomized trial the incidence of CR-POPF after stapler transection with mesh reinforcement was one (1.9%) of 53 patients, significantly reduced from 11 (24%) of 45 patients without mesh reinforcement, but was subject to bias as the study was not blinded (32). Two meta-analyses which included studies using both ISGPS and non-ISGPS definitions for POPF also showed that the reinforced stapler did not reduce the POPF rate compared to the regular stapler (23, 38).

**Question 3:** *Does anastomosis of the pancreatic stump to a Roux-en-Y jejunal limb or as a pancreatogastrostomy impact on the POPF rate after left pancreatectomy in comparison to any of the stump occlusion techniques?*

**Statement 3-1:** Pancreatic anastomosis to a Roux-en-Y jejunal limb does not impact on the POPF rate after left pancreatectomy in comparison with closure techniques.

***Quality assessment: moderate; Recommendation: strong; Agreement: conditional***

**(α= 79.4%).**

**Statement 3-2:** Pancreatic anastomosis with a pancreatogastrostomy does not impact on the POPF rate after left pancreatectomy in comparison with stump closure techniques.

***Quality assessment: moderate; Recommendation: strong; Agreement: conditional***

**(α= 76.4%).**

**Comment**

Pancreatoenteric anastomosis for transection plane management may be undertaken routinely although it is usually undertaken in cases with proximal pancreatic duct obstruction (39), or when closure of the transection plane is technically difficult as when the pancreatic transection is performed on the right side of the portal vein (40). Pancreatoenteric anastomosis techniques include Roux-en-Y pancreatojejunostomy (40-43) or pancreatogastrostomy (44-46) using duct-to-mucosa (40, 43, 44, 46), binding (42) or other techniques (39). The incidence of CR-POPF ranges from zero to up to 60% after pancreatojejunostomy and up to 19.4% after pancreatogastrostomy (15, 40, 42-47).

The results from various studies including randomized trials and metanalyses lack consistency. A meta-analysis by Tieftrunk et al in 2018 found that the CR-POPF rate using pancreatic transection plane anastomosis (8.6%) was significantly lower than suture closure alone (14.6%) with an odds ratio (OR) of 0.36, but was not significantly different (12.1% vs. 13.4%) when compared with the stapler technique (23). Randomized studies however have not shown any statistical difference in POPF between pancreatojejunostomy and other transection plane management techniques (43, 46). Kawai et al found a POPF in 23 (37.7 %) of 61 patients randomized to standard stapler closure and in 24 (38.7%) of 62 patients randomized to pancreatojejunostomy, and for CR-POPF an incidence of 16.4% for stapler closure and 9.7% for pancreatojejunostomy, these differences being statistically not significant (43). A multicentre trial by Uemura et al (2012-2014) found a CR-POPF in 7 (19.4%) of 36 patients randomized to duct-to-mucosa pancreaticogastrostomy versus 7 (18.9%) of 37 patients randomized to pancreatic transection plane handsewn closure. Again these differences were not significantly different (46).

**Question 4:** *Does the use of any energy-based tissue sealing device or additional biological sealant impact on the POPF rate after left pancreatectomy in comparison with the other methods for stump management?*

**Statement 4-1:** The use of an energy-based tissue sealing device does not impact on the POPF rate after left pancreatectomy in comparison with other methods for stump management.

***Quality assessment: moderate; Recommendation: strong; Agreement: strong***

**(α= 88.2%).**

**Statement 4-2:** The use of an additional biologic sealant does not impact on the POPF rate after left pancreatectomy.

***Quality assessment: moderate; Recommendation: strong; Agreement: strong***

**(α= 91.2%).**

**Statement 4-3:** Using the combination of an energy-based tissue sealing device and an additional chemical sealant does not impact on the POPF rate after left pancreatectomyin comparison with other methods for stump management.

***Quality assessment: moderate; Recommendation: strong; Agreement: strong***

**(α= 94.1%).**

***Comment***

The rationale for using energy-generating devices is to cause tissue desiccation and protein coagulation at the cutting surface, which can obliterate the lumen of small vessels and ducts, thus achieving hemostasis and fistula prevention (48). These devices include monopolar electrocautery (49, 50), bipolar electrocautery (48, 51), saline-coupled radiofrequency ablation (17, 52, 53), ultrasonically activated scalpels and dissectors (54, 55).

Ecker et al reported a multinational retrospective study of 2026 left pancreatectomies at 10 institutions. They found closure with an energy sealing device had the highest CR-POPF rate (24.2%) when compared with stapled (12.7%) and handsewn (19.1%) techniques (11). A multicenter randomized trial in 76 patients found a 46.9% POPF rate using a bioabsorbable staple line reinforcement (Seamguard) and 62.9% using a radiofrequency-assisted dissector (TissueLink), with CR-POPF rates of 12.5% and 22.9% respectively, but with no significant differences (56).

In a randomized study a CR-POPF occurred in five (11.4%) of 44 patients who had application of fibrin glue followed by wrapping of a polyglycolic acid mesh around the remnant pancreatic stump, significantly less as compared to 15 in (28.3%) 53 patients who had transection by a stapling device alone (57). Although the application of a collagen sponge with human fibrinogen and thrombin film (TachoSil) may have resulted in a small reduction of grade C POPF in a retrospective study of 36 cases, all the other studies including three randomized trials have shown no benefit in various scenarios following left pancreatectomy including laparoscopic or open surgery and handsewn or staple closure (10, 58-61). In the meta-analysis directly comparing TachoSil versus no TachoSil by Tieftrunk et al however, comprising five studies with 839 patients, including three randomized trials with 646 patients, there was no significant reduction in POPF or CR-POPF using TachoSil (33).

***Question 5:*** *Does ligation of the main pancreatic duct decrease the POPF rate after left pancreatectomy?*

**Statement 5-1:** Ligation of main pancreatic duct decreases the POPF rate after left pancreatectomy.

***Quality assessment: moderate; Recommendation: strong; Agreement: conditional***

**(α= 73.5%).**

**Comment**

Ligation or transfixion of the main pancreatic duct is frequently used to prevent the leaking of pancreatic juice from the cut end of the residual pancreas after left pancreatectomy, either with handsewn closure (4, 5, 9, 21, 25, 41, 42, 46, 62, 63), stapling (9, 21, 64-66), or sealing with energy devices (20, 48-50, 54, 67). Ligation of the main pancreatic duct without transection plane closure has resulted in CR-POPF rates of 35-47.1% (9, 68). In the study from MGH, Boston (1994 – 2008) in 227 patients who had fish mouth transection plane closure, POPF occurred in 46 (29%) of 158 patients that had pancreatic duct ligation and in 21 (30%) of 69 patients who did not (4). Additional retrospective studies have also found that stump closure with or without separate ligation of main pancreatic duct by hand sewing (10, 21, 63, 69), or main duct ligation after stapler transection of the stump, did not impact on the POPF rate (65). Other studies however, report that non-ligation of the main pancreatic duct is a major risk factor for overall POPF or CR-POPF after left pancreatectomy (64, 70, 71). Currently, there is no randomized trial on this topic.

***Question 6:*** *Does prophylactic trans-papillary main pancreatic duct stenting impact on the POPF rate after left pancreatectomy?*

**Statement 6-1:** Prophylactic trans-papillary main pancreatic duct stenting decreases the POPF rate after left pancreatectomy.

***Quality assessment: moderate; Recommendation: weak; Agreement: weak* (α= 32.4%).**

**Comment**

Prograde drainage through the ampulla of Vater may be achieved by placement of an internal transpapillary stent, either intraoperatively (48, 72), or endoscopically preoperatively, resulting in CR-POPF rates ranging from zero to 42.3% and with a risk of acute pancreatitis (25, 73, 74). A randomized trial by Frozanpor et al showed that CR-POPF occurred in 11 (42.3%) of 29 patients who had intra-operative transpapillary pancreatic stenting which was not significantly higher when compared to 6 (22.2%) of 29 patients without stenting (74). A meta-analysis combining this controlled trial with three other retrospective studies for a total of 200 patients, suggested a reduction in POPF in favor of transpapillary main pancreatic duct stenting but there was significant heterogeneity due to the randomized trial of Frozanpor et al, thus calling into question any findings (75).

***Question 7:*** *Does prophylactic botulinum toxin injection into the sphincter of Oddi decrease the POPF rate after left pancreatectomy?*

**Statement 7-1:** Prophylactic botulinum toxin injection into the Sphincter of Oddi decreases the POPF rate after left pancreatectomy.

***Quality assessment: weak; Recommendation: weak; Agreement: weak* (α= 23.5%).**

***Comment***

The sphincter of Oddi is richly innervated by cholinergic, adrenergic and peptidergic neurons and is amenable to pharmacological manipulation including nitrites, Ca2+ channel blockers, and smooth muscle relaxants. Opiates will elevate the sphincter baseline pressure, whilst CCK octapeptide, glucagon and secretin will decrease the baseline pressure. Botulinum toxin produced by Clostridium botulinum is also a potent inhibitor, blocking acetylcholine release from neuromuscular presynaptic nerve endings (76, 77). Increased opioid administration, has been implicated as a risk factor for CR-POPF in various studies of patients with left pancreatectomy (11, 25, 69). A phase I/II trial from Heidelberg of preoperative endoscopic sphincter botulinum toxin injection in 24 consecutive cases of left pancreatectomy showed a 29% biochemical POPF rate but no cases of CR-POPF (77). Approval has now been given for a phase III trial led from Heidelberg.

***Question 8:*** *Can additional coverage of the pancreatic stump with a patch decrease the POPF rate after left pancreatectomy?*

**Statement 8-1:** Additional coverage of the pancreatic stump with an autologous patch decreases the POPF rate after left pancreatectomy.

***Quality assessment: moderate; Recommendation: conditional; Agreement: weak* (α= 47.1%).**

**Comment**

Closure of the pancreatic transection plane can be supplemented with the application of a prosthetic bioabsorbable material, or autologous augmentation using a seromuscular gastric or jejunal patch, a ligamentum teres and falciform ligament patch, or an omental patch (3). A cohort study of 462 consecutive patients from MGH, Boston (1994 – 2008) found a POPF in 133 (29%) patients in the whole series including 30 (28%) of 108 patients who had a falciform patch (4). POPF occurred in 15 (33%) of 45 patients using staple line reinforcement compared to 10 (24%) of 41 patients using the standard stapled technique (4). On multivariate analysis, a body mass index >30 kg/m2, male gender, and an additional procedure were the only significant predictors of pancreatic fistula (4).

In a retrospective study, covering of the pancreatic transection plane using an autologous gastric wall patch was associated with a POPF in one (5.0%) of 20 patients compared to 12 (36.4%) of 33 patients without (78), whilst another retrospective study in 74 patients found no benefit when the transection plane was covered by a gastric or omental patch (79). Furthermore in a randomized trial CR-POPF was found in two (5.7%) of 35 patients who had a stapled resection plus a jejunal seromuscular patch, with no significantly difference when compared to five (14.3%) of 35 patients using the stapling technique alone (66).

Several small studies have suggested that the CR-POPF rate using a ligamentum teres and falciform ligament autologous patch to be relatively low following a left pancreatectomy (80-82). The Thomas Jefferson unit (2008-2011) conducted the first of two randomized trials, allocating 55 patients to stapled or sutured closure and 54 patients to stapled or sutured closure plus a ligamentum falciform patch and fibrin glue reinforcement but subsequently excluded 8 patients with a hard gland from the analysis (83). The POPF rate in patients randomized to the standard techniques was 19.6 % versus 20% in those randomized to have falciform patch and fibrin glue reinforcement (83). The DISCOVER randomized trial from Heidelberg (2010-2014) had two equal groups of 76 patients undergo closure of the pancreatic cut margin with or without teres ligament coverage (84). A CR-POPF occurred in 17 (22.4%) patients with a patch compared to 25 (32.9%) patients without a patch, the difference which was significant on multivariate but not univariate analysis (84).

Velanovich reported no leaks after laparoscopic left pancreatectomy with closure supplemented by an omental patch compared to three (23%) in 13 patients who underwent laparoscopic distal pancreatectomy with standard closure but there have been no large series reported (85). Application of autologous falciform ligament or seromuscular patches was also significantly (OR = 0.49) associated with a lower CR-POPF rate (12.9%) than no patch (20.4%) (23).

***Question 9:*** *Does routine abdominal drainage after left pancreatectomy impact on the likelihood of the POPF rate and/or other postoperative complications?*

**Statement 9-1:** Routine abdominal drainage increases the likelihood of POPF and other postoperative complications including collections, after left pancreatectomy.

***Quality assessment: moderate; Recommendation: conditional; Agreement: weak* (α= 44.1%).**

**Comment**

Several retrospective studies have reported conflicting results on the routine or selective use of intraabdominal drains following left pancreatectomy (11). A major randomized study of 344 patients undergoing left pancreatectomy at 14 high-volume USA pancreas centers found a CR-POPF in 31 (18%) of 174 patents with a drain, which was not significantly different from 20 (12%) of 170 patients with no drain (86). There was also no significant difference in the rate of grade 2 or higher-grade complications (44% vs. 42%), and mortality (0% vs 1% respectively), but omitting routine intraperitoneal drainage was associated with a higher incidence of intra-abdominal fluid collections (22%) than with drainage (9%) (86).

***Question 10:*** *Does the use of prophylactic somatostatin analogues impact on the POPF rate and/or other postoperative complications after left pancreatectomy?*

**Statement 10-1:** The use of prophylactic somatostatin analogues does not reduce the POPF rate and other postoperative complications after left pancreatectomy.

***Quality assessment: moderate; Recommendation: conditional; Agreement: conditional* (α= 67.1%).**

**Comment**

The outcome of studies testing the use of prophylactic somatostatin analogues aimed at reducing POPF and other postoperative complications after left pancreatectomy is conflicting. Explorative analyses of the DISPACT and DISCOVER trials did not show a statistical correlation between the use of somatostatin or its analogues and decreased POPF occurrence (22, 84). In a USA randomized trial, pasireotide resulted in a grade 3 (i.e. requiring drainage) or higher POPF in three (7.3%) of 41 patients after left pancreatectomy, significantly less than in six (15.4%) of 39 patients given a control injection (87).

***Question 11:*** *Are there any clinically significant patient-related risk factors associated with the POPF rate and/or other postoperative complications after left pancreatectomy?*

**Statement 11-1:** There are one or more clinically significant patient-related risk factors associated with the POPF rate and other postoperative complications after left pancreatectomy.

***Quality assessment: moderate; Recommendation: strong; Agreement: strong* (α= 91.2%).**

**Comment**

Kelly et al used the American College of Surgeons National Surgical Quality Improvement Program participant use file (PUF) to analyze 30-day morbidity in 2,322 patients who had left pancreatectomy (2005-2008) (88). The overall 30-day complication rate was 28.1%, including serious complications in 22.2%, most commonly sepsis (8.7%), surgical site infection (5.9%), pneumonia (4.7%) and mortality in 1.2% (88). Preoperative variables associated with morbidity included male gender, high body mass index, smoking, steroid use, neurologic disease, preoperative sepsis, hypoalbuminemia, elevated creatinine, and abnormal platelet count, although it should be noted that the National Surgical Quality Improvement Program does not record pancreatic fistula rates (88). Specific patient related risk factors for POPF following left pancreatectomy include male gender (4, 21), smoking (21), diabetes mellitus (31), body mass index ≥ 25 (4, 25), hypertension (89), decreased albumin level (62), and a low nutritional risk index, based on serum albumin and body weight change (90).

The risk for overall POPF following left pancreatectomy is reduced for pancreatic ductal adenocarcinoma (69), but increased for neuroendocrine and pre-malignant tumors (11) as well as left pancreatectomy for trauma (21).

The texture of the pancreas parenchyma may also affect the fistula rate including an increased risk of CR-POPF with a soft gland (25), less fibrosis (91), and increased fatty infiltration (92).

In a study of 219 patients with a CR-POPF rate of 10% after laparoscopic left pancreatectomy, Weber et al identified greater estimated blood loss (>150 mL), a higher body mass index (>27), and a longer length of resected pancreas (>8 cm) as independent risk factors (93). A meta-analysis including 20 studies with 2070 patients indicated that patients with higher body mass index had a decreased risk for POPF (94), while a soft pancreas, blood transfusion, elevated intra-operative blood loss and a longer operative time were also reported as protective factors for POPF, but included some studies that did not use the ISGPS POPF definition. Moreover the presence of diabetes mellitus, preoperative serum albumin levels, the presence of chronic pancreatitis and the use of biodegradable polyglycolic acid felt wrapping did not influence the POPF rate (94).

The development of a reliable risk prediction score that incorporates individual risk factors is an unmet priority. In the largest study by Ecker et al, with 2026 left pancreatectomies that involved 52 surgeons at 10 institutions, none of the key risk factors including the method of transection, suture ligation of the pancreatic duct, staple size, the use of staple line reinforcement, tissue patches, biologic sealants, or prophylactic octreotide were independently associated with CR-POPF (11), Whilst intraoperative drainage was associated with a greater fistula rate fistula severity rate was significantly less (11).

***Question 12:*** *Does the thickness and texture of the pancreas determine the selective use of the stapling technique for stump closure after left pancreatectomy?*

**Statement 12-1:** A stapling technique cannot be used in all cases of left pancreatectomy because of variations in pancreatic size and texture.

***Quality assessment: weak; Recommendation: conditional; Agreement: strong* (α= 94.1%).**

**Comment**

The thickness as well as the consistency of the pancreas gland seem to affect the effectiveness of stapler transection during left pancreatectomy (26, 95-97). A thicker pancreas appears to be associated with an increased risk of POPF or CR-POPF after stapler transection, but not with other techniques (20, 43, 45, 49, 95-97). High level research on which cartridges are suitable for different thicknesses of pancreatic gland is lacking. To begin to address this problem Kim et al from the Seoul National University Hospital, Korea undertook a systematic prospective study (2011-2015) of 217 consecutive patients who had a left pancreatectomy using a 3-layer endoscopic staple closure (96). A POPF developed in 130 (59.9%) patients, grade A in 86 patients, and grade B in 44 patients. Independent risk factors for POPF were a high body mass index, a thick pancreas, and a high compression ratio defined as pancreas thickness/closure height of the staples (96). There were three groups of staplers based on the closed staple height (≤1.5 mm, 1.5 mm to < 2 mm, and ≥ 2 mm), and pancreatic thickness was grouped into <12 mm, 12-17 mm, and >17 mm. The POPF rate (27.6%) was lowest with a pancreas gland thickness of <12 mm using a 1.5 mm to < 2 mm stapler, the POPF rate was 50% using a ≤1.5 mm stapler, and 69.2% using a ≥ 2 mm stapler. There were no suitable cartridge sizes for thicker pancreata (96).

***Question 13:*** *Does the extent and/or complexity of left pancreatectomy, such as multi-visceral resection impact on the POPF rate and/or other postoperative complications?*

**Statement 13-1:** The extent or complexity of left pancreatectomy including multi-visceral resectiondoes not impact on the POPF rate and/or other postoperative complications, including hemorrhage.

***Quality assessment: moderate; Recommendation: conditional; Agreement: weak* (α= 50.0%).**

**Comment**

A longer operation time has been reported as independent risk factor for POPF (15, 98), CR-POPF (9, 45, 62, 63, 81, 99), or overall complications (19, 88) after left pancreatectomy. Increased blood loss and a higher requirement for blood transfusion during surgery are associated with an increased risk of CR-POPF and other complications (25, 81, 88). Multi-organ resection is associated with increased POPF or CR-POPF rates in some studies (4, 15, 100), but not others (9, 12, 19, 21, 30, 36, 68, 69, 84). Combined vascular resection was found to be independently related to the development of CR-POPF in one study (11) and extended lymphadenectomy in another (64). Overall complications may also be increased by multi-visceral resection during left pancreatectomy (19, 39).

***Question 14:*** *Do different surgical approaches and/or procedures impact on the POPF rate and/or other postoperative complications after left pancreatectomy?*

**Statement 14-1:** There is no difference in the POPF rate and/or POPF-related postoperative complications after left pancreatectomy comparing the open and the laparoscopic or robotic approaches.

***Quality assessment: strong; Recommendation: conditional; Agreement: strong* (α= 88.2%).**

**Statement 14-2:** There is an increased risk of POPF after left pancreatectomy if the transection line goes to the right of the superior mesenteric vein-hepatic portal vein confluence.

***Quality assessment: strong; Recommendation: conditional; Agreement: conditional* (α= 79.4%).**

**Statement 14-3:** There is an increased risk of POPF after left pancreatectomy if the transection line goes towards the splenic hilum.

***Quality assessment: weak; Recommendation: weak; Agreement: weak* (α-score = 38.2%)**

**Comment**

*Laparoscopic versus Robotic versus Open approaches*

Relatively large series of laparoscopic left pancreatectomy, showed an overall complication rate of 26%-55%, a severe complication rate of 8.5%-20%, a POPF rate of 11.3%-45.1% with CR-POPF rate of 3.3%-28%, as well intra-abdominal collections/abscesses of 6%-8% and a need for interventional drainage in 6-11% (99, 101-111). Relatively large series of robotic left pancreatectomy have shown comparable morbidity rates including overall complication rates of 25.6%-72%, major complication rates of 4.9%-14%, POPF rates of 13.0%-42% with CR-POPF rates of 4.3%-18%, intra-abdominal infections of 7%, and the need for interventional drainage of 10% (112-116).

Comparative studies of open versus laparoscopic left pancreatectomy have not revealed any significant differences for the risks of POPF and/or CR-POPF, nor in the incidence of intra-abdominal collections/abscess, and the need for percutaneous drainage (10, 107, 108). Robotic left pancreatectomy has also been reported to have similar rates of POPF, CR-POPF, intra-abdominal infection, and requirement for percutaneous drainage when compared with the laparoscopic left pancreatectomy (115-117). Comparative studies of laparoscopic and robotic left pancreatectomy have also shown similar rates for POPF and CR-POPF when compared with the open surgery (11, 69).

A retrospective cohort study of 928 patients who had elective left pancreatectomy was performed at 106 USA centers in 2014, using the pancreas-targeted American College of Surgeons' National Quality Improvement Program database (118). There were no significant differences in morbidity between the 472 patients that had open left pancreatectomy compared to the 456 patients who had laparoscopic or robotic left pancreatectomy (118). The only independent risk factor for composite major morbidity was a multivisceral procedure (OR = 0.31) (118). The multicenter LEOPARD trial performed on 108 patients, 57 allocated to open and 51 allocated to minimally invasive left pancreatectomy in 14 Netherlands centers (2015-2017) failed to show a significant reduction in the overall rate of complications in the minimally invasive group (119).

A meta-analysis comparing open with laparoscopic left pancreatectomy comprising 29 observational studies with 3701 patients, showed no significant differences in overall morbidity (38.1% vs. 34.3%, respectively) (120). In the meta-analysis by Tieftrunk et al, the choice between open and laparoscopic left pancreatectomy also did not significantly affect the POPF rate (35.3% vs. 43.3%, respectively), or the CR-POPF rate (13.6% vs. 20.0%, respectively) (23). Another meta-analysis. comparing robotic and laparoscopic left pancreatectomy also found no significant differences in the POPF rate (28.6% vs. 28.4%, respectively) or in major morbidity (16% vs. 17%, respectively) (121).

*Position of the transection line*

Some studies suggest that leaving more functioning parenchyma behind following a left pancreatectomy may predispose to POPF (36). The results from various other studies cast uncertainty on this observation (11, 69, 71). Moreover Ban et al reported that pancreatic transection to the right of the portal vein was associated with a significantly increased risk of CR-POPF (9). This might be related to the greater technical difficulty in achieving secure closure of the pancreatic remnant when it forms part of the head of the pancreas.

A summary of domains, questions and results is shown in Table 1 and details of the randomized controlled trials on transection plane management after left pancreatectomy are shown in Table 2 .

In order to ascertain potential bias of the ISGPS participants of this report a further question was asked on the preferred means of transection (voting just for one):

 Scalpel
 Electrocautery
 Stapled transection
 Energy devices
 Other

This revealed

**DISCUSSION**

The development of these guidelines has highlighted the highly complex surgical challenges facing left pancreatectomy. Despite numerous approaches to minimize post-operative complications, left pancreatectomy is associated with a risk for CR-POPF and associated morbidity. The approach we have taken in these guidelines was to evaluate the degree of consensus in the management of left pancreatectomy. We have identified a number of areas with poor agreement, which in itself is extremely important in highlighting particular topics that require focus and intensive research.

There was strong agreement with alpha scores exceeding 80% in six areas which should lead to a significant change in certain aspects of clinical practice. The variable strength of consensus across all of the fourteen domains was closely associated with the strength of scientific evidence for each area. There was strong agreement that there is no difference in the POPF rate after left pancreatectomy between the handsewn and stapler techniques and that a stapling technique cannot be used in all cases of left pancreatectomy because of variations in pancreatic size and texture. A survey led by the International Hepato-Pancreato-Biliary Association (IHPBA), and sister organizations in North America, Europe, Asia and the Far East, showed that stapling techniques were used by 66.3% of the 797 surgeons who responded (3). Given the cost implication of stapler devices there should be some re-evaluation as to its continued use, especially in open left pancreatectomy. There is a proviso in that staplers can facilitate certain technical aspects of a left pancreatomy such as transection of the splenic hilum for spleen preservation and need to remain part of the surgeon’s armamentarium. Staplers are also largely requisite for minimally invasive surgery approaches, rather than hand sewn closures.

There was a strong consensus that the use of an energy-based tissue sealant, use of an additional chemical sealant device, or combinations of these, do not impact on the POPF rate after left pancreatectomy in comparison with other methods for transection plane management. In the IHPBA survey the frequency of use of biological sealants was occasionally (1-25%) in 20.4%, sometimes (26-75%) in 8.6%, frequently (76-99%) in 7.5%, always in 4.3% and never used in the remainder (59.2%) (3).

There was a strong consensus that there is no difference in the POPF rate and/or POPF-related postoperative complications after left pancreatectomy between the open and the laparoscopic or robotic approaches, so it is incumbent on the proponents of the laparoscopic and robotic techniques to provide evidence covering the other advantages that minimally invasive approaches might provide.

The agreement that there are one or more clinically significant patient-related risk factors associated with the POPF rate and other postoperative complications after left pancreatectomy means that such factors must enter into the planning of prospective studies and be routinely reported in publications. The development of a robust risk score for prediction of CR-POPF would be of considerable value. A separate consensus agreement is required to determine the minimum set of risk factors to be reported.

In addition, there were eight of the remaining 14 domains in which there was only conditional or weak agreement. The corollary is that not only are novel approaches required but that large multicenter studies need to be coordinated to provide fundamental answers to key areas of practice which include choices regarding the use of prophylactic somatostatin analogues, pancreatic stents, anastomosis to the transection plane, techniques for stump closure, and the role of abdominal drains.

**CONFLICT OF INTEREST**

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**Table 1.** Summary of domains, questions and results.

|  |  |
| --- | --- |
| **Question 1** | *Does either the handsewn technique or the stapler technique for stump closure after left pancreatectomy reduce the POPF rate compared to each other or other methods?* |
| **Statement 1-1** | There is no difference in the POPF rate after left pancreatectomy between the handsewn and stapler techniques.***Quality assessment: high; Recommendation: strong; Agreement: strong* (α=94.1%).** |
| **Statement 1-2** | Specifically, the handsewn fish-mouth technique does not decrease the POPF rate after left pancreatectomy compared to other techniques.***Quality assessment: moderate; Recommendation: strong; Agreement: conditional* (α=79.4%).** |
| **Question 2** | *Does the reinforced stapler technique reduce the POPF rate after left pancreatectomy when compared with the regular stapler.* |
| **Statement 2-1** | The reinforced stapler technique reduces the CR-POPF rate after left pancreatectomy in comparison with the regular stapler technique.***Quality assessment: moderate; Recommendation: conditional; Agreement: weak* (α=61.8%).** |
| **Question 3** | *Does anastomosis of the pancreatic stump to a Roux-en-Y jejunal limb or as a pancreatogastrostomy impact on the POPF rate after left pancreatectomy in comparison to any of the stump occlusion techniques?* |
| **Statement 3-1** | Pancreatic anastomosis to a Roux-en-Y jejunal limb does not impact on the POPF rate after left pancreatectomy in comparison with closure techniques. ***Quality assessment: moderate; Recommendation: strong; Agreement: conditional*****(α= 79.4%).** |
| **Statement 3-2** | Pancreatic anastomosis with a pancreatogastrostomy does not impact on the POPF rate after left pancreatectomy in comparison with stump closure techniques. ***Quality assessment: moderate; Recommendation: strong; Agreement: conditional*****(α= 76.4%).** |
| **Question 4** | *Does the use of any energy-based tissue sealing device or additional biological sealant impact on the POPF rate after left pancreatectomy in comparison with the other methods for stump management?* |
| **Statement 4-1** | The use of an energy-based tissue sealing device does not impact on the POPF rate after left pancreatectomy in comparison with other methods for stump management. ***Quality assessment: moderate; Recommendation: strong; Agreement: strong*****(α= 88.2%).** |
| **Statement 4-2** | The use of an additional biologic sealant does not impact on the POPF rate after left pancreatectomy. ***Quality assessment: moderate; Recommendation: strong; Agreement: strong*****(α= 91.2%).** |
| **Statement 4-3** | Using the combination of an energy-based tissue sealing device and an additional chemical sealant does not impact on the POPF rate after left pancreatectomyin comparison with other methods for stump management. ***Quality assessment: moderate; Recommendation: strong; Agreement: strong*****(α= 94.1%).** |
| **Question 5** | *Does ligation of the main pancreatic duct decrease the POPF rate after left pancreatectomy?* |
| **Statement 5-1** | Ligation of main pancreatic duct decreases the POPF rate after left pancreatectomy. ***Quality assessment: moderate; Recommendation: strong; Agreement: conditional*****(α= 73.5%).** |
| **Question 6** | *Does prophylactic trans-papillary main pancreatic duct stenting impact on the POPF rate after left pancreatectomy?* |
| **Statement 6-1** | Prophylactic trans-papillary main pancreatic duct stenting decreases the POPF rate after left pancreatectomy. ***Quality assessment: moderate; Recommendation: weak; Agreement: weak* (α= 32.4%).** |
| **Question 7** | *Does prophylactic botulinum toxin injection into the sphincter of Oddi decrease the POPF rate after left pancreatectomy?* |
| **Statement 7-1** | Prophylactic botulinum toxin injection into the Sphincter of Oddi decreases the POPF rate after left pancreatectomy. ***Quality assessment: weak; Recommendation: weak; Agreement: weak* (α= 23.5%).** |
| **Question 8** | *Can additional coverage of the pancreatic stump with a patch decrease the POPF rate after left pancreatectomy?* |
| **Statement 8-1** | Additional coverage of the pancreatic stump with an autologous patch decreases the POPF rate after left pancreatectomy. ***Quality assessment: moderate; Recommendation: conditional; Agreement: weak* (α= 47.1%).** |
| **Question 9** | *Does routine abdominal drainage after left pancreatectomy impact on the likelihood of the POPF rate and/or other postoperative complications?* |
| **Statement 9-1** | Routine abdominal drainage increases the likelihood of POPF and other postoperative complications including collections, after left pancreatectomy. ***Quality assessment: moderate; Recommendation: conditional; Agreement: weak* (α= 44.1%).** |
| **Question 10** | *Does the use of prophylactic somatostatin analogues impact on the POPF rate and/or other postoperative complications after left pancreatectomy?* |
| **Statement 10-1** | The use of prophylactic somatostatin analogues does not reduce the POPF rate and other postoperative complications after left pancreatectomy. ***Quality assessment: moderate; Recommendation: conditional; Agreement: conditional* (α= 67.1%).** |
| **Question 11** | *Are there any clinically significant patient-related risk factors associated with the POPF rate and/or other postoperative complications after left pancreatectomy?* |
| **Statement 11-1** | There are one or more clinically significant patient-related risk factors associated with the POPF rate and other postoperative complications after left pancreatectomy. ***Quality assessment: moderate; Recommendation: strong; Agreement: strong* (α= 91.2%).** |
| **Question 12** | *Does the thickness and texture of the pancreas determine the selective use of the stapling technique for stump closure after left pancreatectomy?* |
| **Statement 12-1** | A stapling technique cannot be used in all cases of left pancreatectomy because of variations in pancreatic size and texture. ***Quality assessment: weak; Recommendation: conditional; Agreement: strong* (α= 94.1%).** |
| **Question 13** | *Does the extent and/or complexity of left pancreatectomy, such as multi-visceral resection impact on the POPF rate and/or other postoperative complications?* |
| **Statement 13-1** | The extent or complexity of left pancreatectomy including multi-visceral resectiondoes not impact on the POPF rate and/or other postoperative complications, including hemorrhage. ***Quality assessment: moderate; Recommendation: conditional; Agreement: weak* (α= 50.0%).** |
| **Question 14** | *Do different surgical approaches and/or procedures impact on the POPF rate and/or other postoperative complications after left pancreatectomy?* |
| **Statement 14-1** | There is no difference in the POPF rate and/or POPF-related postoperative complications after left pancreatectomy comparing the open and the laparoscopic or robotic approaches. ***Quality assessment: strong; Recommendation: conditional; Agreement: strong* (α= 88.2%).** |
| **Statement 14-2** | There is an increased risk of POPF after left pancreatectomy if the transection line goes to the right of the superior mesenteric vein-hepatic portal vein confluence. ***Quality assessment: strong; Recommendation: conditional; Agreement: conditional* (α= 79.4%).** |
| **Statement 14-3** | There is an increased risk of POPF after left pancreatectomy if the transection line goes towards the splenic hilum. ***Quality assessment: weak; Recommendation: weak; Agreement: weak* (α-score = 38.2%)** |

**Table 2.** Randomised controlled trials on transection plane (stump) management after left pancreatectomy.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **First author, Year** | **Country** | **Setting** | **Number of participants** | **Intervention** | **Primary endpoint** | **Effects of intervention on primary endpoint and POPF** | **Conclusion** |
| Diener MK, 2011 (22) | Europe | Multicenter | 177:175 | Stapler vs. handsewn closure | ISGPS \*POPF + Death | 56/177 vs. 49/175, OR=0·84 (95%CI: 0·53–1·33) | Stapler closure did not reduce POPF compared with hand-sewn closure in LP |
| Hamilton NA, 2012 (32) | USA | Single center | 46:54 | Regular stapler vs. reinforced stapler closure | ISGPS †CR-POPF | 1/53 vs. 11/45, p = 0.0007 | Mesh reinforcement reduced CR-POPF after ‡LP |
| Kawai M,2016 (43) | Japan | Multicenter | 61:62 | Stapler closure vs. pancreatojejunostomy | ISGPS POPF | 23/61 vs. 24/62 | Pancreatojejunostomy of the pancreatic stump during LP does not reduce pancreatic fistula compared with stapler closure. |
| Uemura K,2017 (46) | Japan | Multicenter | 36:37 | Duct-to-mucosa pancreatogastrostomy vs. handsewn closure | ISGPS CR-POPF | 7/36 vs. 7/37, §OR=1.03, ||NS | Duct-to-mucosa pancreatogastrostomy did not reduce CR-POPF compared with handsewn closure in LP |
| Shubert CR, 2016 (56) | USA | Multicenter | 32:35 | Reinforced stapler closure vs. TissueLink without stump closure | ISGPS POPF | 15/32 vs. 22/35, NS | No difference in POPF was seen between reinforced stapler and TissueLink in closing pancreatic stump during LP |
| Frozanpor F,2012 (74) | Sweden | Single center | 26:27 | Intra-operative transpapillary pancreatic stenting vs. no stenting (both with stapler closure) | ISGPS POPF | 13/26 vs. 10/27, NS.; CR-POPF: 11/26 vs. 6/27, NS | Prophylactic transpapillary pancreatic stenting did not reduce POPF in LP |
| Jang JY,2017 (57) | Korea | Multicenter | 44:53 | Polyglycolic acid mesh vs. no mesh (both with stapler closure) | ISGPS CR-POPF | 5/44 vs. 15/53, p = 0.04 | Wrapping of the cut surface of the pancreas after LP with polyglycolic acid mesh was associated with a significantly reduced CR-POPF rate. |
| Sa Cunha A, 2015 (10) | Europe | Multicenter | 134:136 | TachoSil patch vs. no TachoSil | ISGPS CR-POPF | 41/134 vs. 33/136, NS | TachoSil sponge reinforcement of the proximal remnant after LP reduced neither the rate nor the severity of POPF. |
| Montorsi M, 2012 (61) | Italy | Multicenter | 145:130 | TachoSil patch vs. no TachoSil | ISGPS POPF | 90/145 vs. 89/130, NS; CR-POPF: 12/145 vs. 18/130, NS | TachoSil had no significant effect on the rate of POPF after LP. |
| Park JS,2016 (60) | Korea | Multicenter | 48:53 (per protocol) | TachoSil patch vs. no TachoSil | ISGPS POPF | 34/48 vs. 29/53, NS; CR-POPF: 11/48 vs. 15/58, NS | TachoSil did not reduce the incidence of POPF after LP. |
| Oláh A,2009 (66) | Hungary | Single center | 35:35 | Jejunal seromuscular patch vs. no patch (both with stapler closure) | ISGPS POPF and/or intraabdominal fluid collection | 4/35 vs. 11/35, p = 0.041; 1/35 vs/ 3/35, NS | Covering the stapled pancreatic remnants with a seromuscular patch decreased overall pancreas-related complications such as fistula. |
| Carter TI,2013 (83) | US | Single center | 50:51 | Devascularized falciform ligament + fibrin glue coverage vs. no coverage | ISGPS POPF | 10/50 vs. 10/51, NS | The addition of a falciform ligament patch and fibrin glue to standard stapled or sutured remnant closure did not reduce the rate or severity of POPF after LP. |
| Hassenpflug M,2016 (84) | Germany | Single center | 76:76 | Teres ligament coverage vs. no coverage | ISGPS POPF | 36/76 vs. 39/76, NS; CR-POPF: 17/76 vs. 25/76, NS | Coverage of the pancreatic remnant after LP is associated with less reinterventions, reoperations, and need for readmission, but not less POPF. |
| Van Buren G 2nd,2017 (86) | USA | Multicenter | 174:170 | Prophylactic intraabdominal drainage after LP vs. no drainage | 60-day ≥ grade 2 complication rate | 76/174 vs. 72/170, NS; CR-POPF: 31/174 vs. 20/170, p = 0.114 | Clinical outcomes were comparable in LP with or without intraperitoneal drainage |
| Allen PJ,2014 (87) | USA | Single center | 41:39 | Prophylactic pasireotide treatment vs. no pasireotide treatment | 60-day ≥grade 3 pancreatic fistula, leak or abscess | 3/41 vs. 6/39, p = 0.006 | Perioperative treatment with pasireotide decreased the rate of clinically significant postoperative pancreatic fistula, leak, or abscess after LP. |
| de Rooij T,2018 (119) | The Netherlands | Multicenter | 51:57 | Minimally-invasive LP vs. open LP | Time to functional recovery after surgery | 4(3-6) vs. 6(5-8) days, p < 0.001; CR-POPF: 20/51 vs. 13/57, ¶RR = 1.72 (0.96-3.09), NS  | Minimally-invasive reduced time to functional recovery, but not overall rate of complication and POPF. |

\*POPF=postoperative pancreatic fistula; †CR= clinically related; ‡LP = left pancreatectomy; §OR = odds ratio; ||NS = not significant; ¶RR = relative ratio.