Laparoscopic distal pancreatectomy: better than open?

Abe Fingerhut¹, Selman Uranues¹, Igor Khatkov², Luigi Boni³

¹Section for Surgical Research, Department of Surgery, University of Graz, Graz, Graz, Austria; ²Department of Surgical Oncology Moscow Clinical Scientific Center, Moscow, Russia; ³Department of Surgery, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, University of Milan, Milan, Italy

Contributions: (I) Conception and design: A Fingerhut, S Uranues, I Khatkov; (II) Administrative support: A Fingerhut, S Uranues; (III) Provision of study materials or patients: A Fingerhut, L Boni; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Abe Fingerhut. Section for Surgical Research, Department of Surgery, University of Graz, Graz, Austria. Email: abefingerhut@aol.com.

Abstract: Distal pancreatectomy is well suited to the laparoscopic approach. Laparoscopic distal pancreatectomy (LDP) provides the same postoperative recovery advantages reputed to minimal access surgery. However, there have been fears as to the safety of LDP in terms of life-threatening intra-operative events and post-operative complications, adequate carcinological outcomes as compared to traditional (open) distal pancreatectomy (ODP) when performed for cancer, as well as to whether the laparoscopic approach is well adapted to the variety of diseases that may affect the pancreas (ranging from trauma to benign or malignant disease) and whether the minimal access approach is well adapted to perform pancreatic surgery safely in the obese, the elderly or the frail. In this review of the literature, we sought to determine whether LDP was as safe, provided the same oncological outcomes and was applicable to all diseases involving the body and tail of the pancreas, and to particular patient characteristics, compared to the traditional open approach. Last we looked at cost issues. We concluded that this review of the literature allowed to state that laparoscopic distal pancreatectomy is feasible and safe for a wide range of diseases, both benign and malignant. Morbidity, mortality, and probably, also, carcinological outcomes are comparable to open surgery. The overall costs are similar but the advantages of minimal access surgery make it the preferred approach, once the surgical expertise is acquired and present.

Keywords: Distal pancreatectomy; left pancreatectomy; laparoscopy; laparotomy comparison; meta-analysis

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Introduction

Laparoscopic distal (left) pancreatectomy (LDP) was performed by expert laparoscopic surgeons as early as 1994 (1,2), but the technique took some time to catch on in overall practice. As for other procedures performed laparoscopically (cholecystectomy, colonic disease, hysterectomy), the minimal access approach is likely to reduce pain, decrease blood loss, shorten hospital stay, enhance the postoperative course, and provide better cosmesis and reduced costs (3,4). The laparoscopic approach is well suited to DP because the visual magnification obtained with high definition cameras under laparoscopy lead to more precise and controlled tissue manipulation and facilitates access to the deep posterior aspect of the gland; moreover, there is no need for reconstruction (5).

While LDP should theoretically provide the same postoperative recovery advantages reputed to minimal access surgery, there have been fears as to the safety of LDP in terms of life-threatening intra-operative events and postoperative complications, adequate carcinological outcomes as compared to traditional (open) distal pancreatectomy (ODP) when performed for cancer (6), as well as to whether the laparoscopic approach is well adapted to the variety of diseases that may affect the pancreas (ranging from trauma to benign or malignant disease) and whether the minimal



Figure 1 PRISMA flow chart of selection of articles.

access approach is well adapted to perform pancreatic surgery safely in the obese, the elderly or the frail.

Our goal was to review the literature to determine whether LDP was as safe, provided the same oncological outcomes and was applicable to all diseases involving the body and tail of the pancreas, and amenable to particular patient characteristics, compared to the traditional open approach. Last we looked at cost issues.

Material and methods

We conducted our systematic review of the literature according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (7). EMBASE, Medline, Web of science, Cochrane CENTRAL and Google scholar databases were systematically searched up to March 2018 for articles comparing LDP to ODP using the following terms: laparoscopic distal pancreatectomy, distal pancreatectomy, laparoscopic left pancreatectomy, left pancreatectomy, comparison, pancreas left resection, distal pancreas resection; distal pancreatectomy; left pancreatectomy, laparoscopic surgery, minimally invasive surgery; open surgery; laparotomy. We limited our search to manuscripts written in English.

Results

The initial database search resulted in 53,091 articles. After eliminating publications that could have contained duplicate series or duplicates that arose from searching several data

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bases, 164 potentially relevant articles were screened for appropriateness. Only studies explicitly comparing laparoscopic to open resection were retained. No case series reports were considered.

This resulted in 56 studies available for the systematic review. The PRISMA flowchart presented in *Figure 1* depicts the detailed selection of studies.

Among the 56 studies published in full, none were randomized. There were ten meta-analyses or systematic reviews (8-17) including one Cochrane review (18) with considerable overlap. Because of this overlap, we chose to base the main points of our analysis on the four most recent and/or with the least overlap (10,13,15,18). Three concerned only malignancy (13,14,18).

There are currently six randomized trials underway. To the best of our knowledge, two have been completed (LAPOP and LEOPARD) but only one with available results (not published), the LEOPARD study (de Rooij) (19,20).

The proportion of DP performed via minimal access surgery (MAS) is on the rise, accounting for between 10.8% to 46.6% of DP published worldwide (10,21,22). Responders of a worldwide survey including 435 surgeons from 50 countries reported that they performed a median of 22 (IQR: 0–450) pancreatic resections as primary surgeon yearly (23). Minimal access distal pancreatectomy (MADP) was performed by 345 (79%) of these surgeons. Of these surgeons, 338 (98%) considered the overall value of such resections superior or equivalent to the traditional approach.

Results of the analysis

Indications for laparoscopic distal pancreatectomy

The indications for LDP are similar to those for open distal pancreatectomy (10,24-26): distal pancreatectomy for benign, borderline, or malignant tumors of the pancreatic body and tail, distal pancreatectomy for pancreatic injury and chronic or acute pancreatitis with pseudocyst located in the pancreatic body and tail. Obvious contraindications for LDP include: invasion of surrounding organs or critical vasculature, distant metastasis in cancer (22), or acute pancreatitis (27). Obesity is not a formal contra-indication although it makes the operation more challenging (15,24).

Spleen preserving LDP has been described to be feasible and safe (26,28), being reported in 18.2% (29) to 60.4% (30) of LDPs. Spleen preserving techniques may be easier to perform laparoscopically but the preservation of the short gastric vessels, as required in the Warshaw technique (31), might be more complex to perform laparoscopically (32). As well, radical cancer operations require splenectomy, which can be performed laparoscopically, but this will be discussed later.

Operative times

Several comparative publications reporting on duration of operation have found that there was no statistically significant difference between LDP and ODP, ranging from 156 to 383 min and from 145 to 330 min in laparoscopic and open surgery, respectively (16,29,33,34). However this was not analyzed in the recent Cochrane review of 2016 (18).

Conversion

The conversion rate from laparoscopic to open surgery, collated by Justin *et al.*, varied widely from one series to another 0% to 34% (33-37), hemorrhage and failure to progress being the most common causes.

Morbidity and mortality

Complications after LDP have been reported to range between 0 and 67% in single center studies (28,38). However, several meta-analyses (10,35) and systematic reviews (18) have described overall morbidity ranging from 34% to 37.4%.

In their 2015 meta-analysis of 34 studies (10), Mehrabi *et al.* found a statistically significant difference in time to oral intake (-1.3 days) and duration of stay (-3.8 d). Of note, post-operative stay after DP has been reported to be shorter in the United States when compared to other countries, most likely due to differences in health care systems (35). More recently, Shin and colleagues (22) confirmed these significant reductions associated with LDP single center, propensity matched analysis.

While Riviere *et al.* (18) found a 2.43 days shorter hospital stay for LDP (mean difference -2.43 days, 95% CI, -3.13 to -1.73; 1,068 participants; five studies; $I^2=0\%$), quality of life, time to return to normal activity and time to return to work or blood transfusion requirements were not reported.

The recently finished LEOPARD study (20) (51 LDP vs. 56 ODP in 17 Dutch centers, operated on for symptomatic benign or malignant tumors of the body or tail) found that LDP was statistically significantly associated with less blood loss (150 vs. 400 mL, P<0.001), longer operation time (217 vs. 179 min) (P=0.05), shorter duration of hospital stay {6 [4–7] vs. 8 [6–9] days} [median (IQR)] (P<0.001) and faster functional recovery {4 [3–6] vs. 6 [5–8]} (P<0.001) (defined as patients being independently mobile, adequately controlled for pain, maintaining at least 50 of daily required intake, no need for intravenous administration and no signs of infection). No statistically significant difference was found in morbidity (Dindo/Clavien grade 3 or higher) [13 (25%) vs. 21 (38%)], POPF grades B/C [20 (39%) vs. 13 (23%)] or 90-day mortality [0 (0%) vs. 1 (2%)] (20).

Post-operative pancreatic fistula (POPF)

Morbidity is essentially related to post-operative pancreatic fistula (POPF), wound infection and omental infarction (27). This might explain why there is a wide range of morbidity rates because authors have used many different definitions for POPF in their literature. Adhering to the ISGPF definition, systematic reviews have described the POPF incidence to range from 16.8% to 21.7% in LDP (10-25).

One systematic review and meta-analysis (17) reported that LDP (compared to open, all other factors being equal) was associated with less POPF. This contrasts with the results of the studies by Sa Cunha *et al.* (32) and Cho *et al.* (39), who found that postoperative complications (including POPF) were similar in the two groups. Of note, the metaanalysis (17) included only observational, and heterogeneous studies, while the Central Pancreas Consortium Study (39) encompassed only expert centers, a potential selection bias.

Røsok *et al.* (15) (16 studies) did not find any statistically significant difference in the rates of B/C POPF. Of note, they included three studies that were not included in any of the other meta-analyses (38,40,41).

The Cochrane production on distal pancreatectomy for cancer only (18) analyzed the outcomes of 11 studies (1,506 participants: 353 undergoing laparoscopic distal pancreatectomy and 1,153 undergoing open distal pancreatectomy) providing data for one or more outcomes. The authors were unable to come to any conclusions concerning the differences in short-term or long-term mortality, the proportion of patients with serious or any adverse events, or with a clinically relevant POPF.

Hand-sewn or stapled closures are the most common techniques used for pancreatic remnant management after LDP. While the systematic review of observational studies (42) was in favor of stapled closure, Jensen *et al.* (43) [analysis of 10 studies (five retrospective reviews, five

prospective case series) between 2007 and 2009] found the overall relative risk of developing a POPF following distal pancreatectomy was 1.00 (95% CI, 0.65-1.53). Although no conclusions could be formally proposed, the authors suggested that reinforced staples could be an attractive solution as when only prospective studies were analyzed, the RR was 14.45 (95% CI, 3.15-66.21). Overall, the metaanalysis of Wang et al. (44), two high-volume institutional studies (45,46) and two RCT (42,47) found that stapled stump closure was associated with a slightly higher POPF rate. Two meta-analyses (48,49), one high-volume study (50) and one multicenter (21 European centers) randomized controlled trial (42), however, were not able to show any statistically significant differences in POPF or overall morbidity between the two closure techniques, whether performed by laparoscopy or laparotomy. Of note, several of these studies (42,45,47,48) did not distinguish between clinically silent and clinically relevant POPF. In the Sa Cuhna study on the usefulness of TachoSil to cover the pancreatic stump after division (32), hand-sewn closure of the pancreatic stump and ligation of the splenic vessels in case of splenic preservation were found to have a significant risk for clinically relevant POPF; this is of interest in the modern era where more and more distal pancreatectomies are being performed laparoscopically (46,51) and stapled stump closure and splenic vessel preservation are preferred in laparoscopic distal pancreatectomy (26,27,32).

One of the reasons for the discrepancy of outcome might be the effect of crushing the pancreatic parenchyma by the jaws of the linear stapler. Effectively, when the pancreas is thick (>12 mm), staple closure may in fact increase the POPF rate (52). As recommended in general, gradual closing of the stapler jaws (2–3 minutes) has been reported to decrease POPF (53). More recently, several authors have insisted on the necessity to first gradually crush the future line of resection before actually firing the stapler (54,55).

Older studies reported that reoperation rates (ranging from 2.1% to 6%) (17,35,56) after laparoscopic DP did not differ from outcomes after open surgery.

Several meta-analyses have found that LDP, even with splenectomy, was superior to PDP in terms of intraoperative blood loss and duration of hospital stay (10,16,17) confirming the results of several controlled trials (21,33,57,58) in this sense.

Carcinological concerns

Several experienced (5-28) laparoscopic surgeons have

reported (29-50) that it is easier to achieve an R0 resection with the laparoscopic approach (50-61) while others argue that there is no significant difference in R0 resection rates between laparoscopic or open DP (21,62-64).

Radical operations such as the radical antegrade modular pancreatosplenectomy

RAMP procedure (65), the clockwise procedure (53), are technically challenging laparoscopically, but do appear to be feasible (66,67).

Both the systematic review by Ricci *et al.* (14) and Mehrabi *et al.* (10) confirmed that there was no statistically significant difference in R0 resection rates, lymph node harvest and survival, although they did not include the same studies (five and four studies respectively).

The systematic review by Ricci *et al.* (14) including five studies (58,62,64,68,69) found that R0 resection margins were 86.3% *vs.* 80.7% with an OR of 1.29 (95% CI, 0.59 to 2.82; P=0.53), lymph node retrieval (14.4 \pm 7.3, 13.3 \pm 7.6), and survival (HR of 0.66; 95% CI, 0.29–1.51; P=0.32) between the two groups. The meta-analysis by Mehrabi *et al.* (10) including four studies (63,70-72), reported comparable R0 rates in both groups (592 patients) (OR 1.63; 95% CI, 0.65–4.07; P=0.29), while the rate of R1 resections was lower in the LDP group (520 patients) (OR 0.34; 95% CI, 0.14–0.83; P=0.02) (70,71). None of the studies included in the Riviere Cochrane review reported on recurrence within six months (18).

According to the International Study Group on Pancreatic Surgery guidelines (73), lymph nodes in stations 10, 11, and 18 should be resected during distal pancreatectomy for cancer. Resection of lymph nodes in stations 8a and 9 is optional, but should be included in the resection when cancer is located in the body of the pancreas.

Lee *et al.* (58) reported that the lymph node yield was higher in open surgery as compared to laparoscopic (or robotic) distal pancreatectomy. This contrasts with the other oncological outcomes in this same comparison.

In the review of Wang *et al.* (44), there was no significant difference found in the mean number of lymph nodes harvested between LDP and ODP (12 to 13.8 in LDP *vs.* 10 to 12.5 in ODP) (21,22). However, the median number (10, range 1–64) of lymph nodes harvested in the ODP group in one report (22) was less than 12, the recommended number for adequate disease staging (74).

Shin *et al.* reported a median survival of 33.4 months in LDP vs. 29.1 months in OPD (P=0.025) (22). While

a multicenter study by Kooby *et al.* showed considerably shorter survival (16 months) in both groups (21). While low long-term survival rates are typical for pancreatic cancer, the difference in survival between these last two studies could be related to the differences in median tumor diameter (3.0 *vs.* 3.5 cm) and/or the type of (monocenter *vs.* multicenter) study.

In the Rivière Cochrane review (18), the authors were also unable to come to any formal conclusions concerning the differences in recurrence at maximal follow-up or the proportion of participants with positive resection margins. Thus, the oncological results of LDP in patients with pancreatic ductal adenocarcinoma is unclear. Of note, the lymph node status is an oncologically important variable, as pancreatic ductal adenocarcinoma of the pancreatic body and tail frequently metastasize to regional lymph nodes. In cases of resectable pancreatic ductal adenocarcinoma located in the body and tail, positive lymph nodes are found in 47-80% of resected specimens (75). In the previous report on LDP for exocrine carcinoma from one expert center, a median of 5 [0-26] lymph nodes were found in the specimen; notwithstanding, the 3-year survival was still relatively high (30%) (60). Although a recent metaanalysis of distal pancreatectomy for pancreatic ductal adenocarcinoma suggested that lymph node yields were comparable following laparoscopic or open DP, the small number of cases in laparoscopic group (n=80) limits the reliability of these findings (14).

Performing LDP in patients with obesity was raised as a specific concern in the Minimal Invasive Surgery symposium held in Sao Paulo April 2016 (15). Studies on the impact of obesity on laparoscopic pancreatic resections are few. Of note, in the retrospective cohort study of elective open versus minimal access distal pancreatectomy using the American College of Surgeons' National Quality Improvement Program (ACS-NSQIP) database (106 centers in 2014), only 8% of the respondents considered morbid obesity as a contra-indication for minimal access DP; however, milder forms of obesity were not (15,20,23). In a Dutch nationwide study comparing LDP to ODP, increased BMI was not associated with higher complication rates in the laparoscopic group (40). A Norwegian single high volume center study (76) found that obesity (BMI >30) led to longer operative duration and increased blood loss compared to patients who were overweight (BMI between 25-30) and those whose BMI was 25 or less. There was no statistically significant difference found in duration of hospital stay or complication rates. As noted above, the expert panel agreed that higher BMI could lead to specific challenges, but high BMI alone was not a contra-indication and did not preclude an attempt to perform a LDP.

The same Norwegian group also studied the outcomes of LDP in the elderly and found that LDP was safe in patients aged \geq 70 years, providing outcomes similar to those in younger group (77). In a French multicenter study (78), the laparoscopic approach was associated with reduced blood loss, postoperative confusion, and duration of stay in elderly patients requiring distal pancreatectomy. Overall, these two studies confirm that elderly patients with pancreatic adenocarcinoma can benefit from LDP, since age itself is not associated with decreased survival after surgery.

Costs

Costs were evaluated in a review article by Conlon and the Minimally Invasive Pancreatic Resection Organizing Committee and presented in the International Hepatobiliary and Pancreatic meeting in Sao Paulo on April 20, 2017 (79). Minimally invasive pancreatic resections: cost and value perspectives. Compared to the open approach, minimal access distal pancreatic resections were associated with higher operative costs but lower postoperative costs. Patientrelated values (defined as improvement in both quantity and quality of life) and financial value (using incremental costeffectiveness ratio) remain to be determined.

In conclusion, this review of the literature allows us to state that laparoscopic distal pancreatectomy is feasible and safe for a wide range of diseases, both benign and malignant. Morbidity, mortality, and probably, also, carcinological outcomes are comparable to open surgery. The advantages of minimal access surgery should lead to propose this approach preferentially, once the surgical expertise is acquired and present.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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