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REVIEW

Distal pancreatectomy with or without radical approach, vascular resections and splenectomy: Easier does not always mean easy

Lapo Bencini, Alessio Minuzzo

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Abstract

Because distal pancreatectomy (DP) has no reconstructive steps and less frequent vascular involvement, it is thought to be the easier counterpart of pancreaticoduodenectomy. This procedure has a high surgical risk and the overall incidences of perioperative morbidity (mainly pancreatic fistula), and mortality are still high, in addition to the challenges that accompany delayed access to adjuvant therapies (if any) and prolonged impairment of daily activities. Moreover, surgery to remove malignancy of the body or tail of the pancreas is associated with poor long-term oncological outcomes. From this perspective, new surgical approaches, and aggressive techniques, such as radical antegrade modular pancreato-splenectomy and DP with celiac axis resection, could lead to improved survival in those affected by more locally advanced tumors. Conversely, minimally invasive approaches such as laparoscopic and robotic surgeries and the avoidance of routine concomitant splenectomy have been developed to reduce the burden of surgical stress. The purpose of ongoing surgical research has been to achieve significant reductions in perioperative complications, length of hospital stays and the time between surgery and the beginning of adjuvant chemotherapy. Because a dedicated multidisciplinary team is crucial to pancreatic surgery, hospital and surgeon volumes have been confirmed to be associated with better outcomes in patients affected by benign, borderline, and malignant diseases of the pancreas. The purpose of this review is to examine the state of the art in distal pancreatectomies, with a special focus on minimally invasive approaches and oncological-directed techniques. The widespread reproducibility, cost-effectiveness and long-term results of each oncological procedure are also taken into deep consideration.

Key Words: Distal pancreatectomy; Minimally invasive; Splenectomy; Laparoscopic

Core Tip: Laparoscopic or robotic distal pancreatectomy is a good option to cure diseases arising from the pancreatic body/tail. The minimally-invasive approach allows to achieve concomitant splenectomy and arterial resections. However, current Literature is still lacking, and the surgical decision is based mainly on the presence of advanced laparoscopic and da Vinci equipment, controlled by skillful experts. A rigorous attention to the general and oncologic principles should be the maintained.

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INTRODUCTION

Distal pancreatectomy (DP) should be defined as resection of the pancreatic gland distal to the left mesenteric vein, including the body and tail of the pancreas. Indications for DP include a wide spectrum of diseases, ranging from benign to highly aggressive neoplasms. In the first group, most cases consist of chronic pancreatitis and benign cysts, while pancreatic adenocarcinoma is the most frequent pathology in the second[1]. In selected cases, DP also often requires concomitant splenectomy as a routine step of the same operation.

For pancreatic cancer, long-term survival after DP remains unsatisfactory, with a median survival time of 17-28 mo and a 5-year overall survival of approximately 20%-30%[2,3]. Despite the highly aggressive nature of the disease and early regional lymph node metastasis, adenocarcinomas of the body and tail of the pancreas have attracted significantly less clinical attention than proximal tumors[4].

Traditionally, DP is considered less challenging than pancreaticoduodenectomy, as proven by the reported lower perioperative morbidity and mortality of patients[5,6] due to the lack of reconstructive steps. Moreover, the most important postoperative complication, pancreatic fistula, is rarely life-threatening (1% mortality)[7,8]. A logical consequence of these issues led to investigating the result of minimally invasive DP (MIDP), which has been widely accepted in the worldwide surgical community [9]. Interestingly, after the first procedure reported by Cuschieri *et al*[10], MIDP has now become the procedure of choice in tertiary referral centers for both benign and malignant lesions of the body and tail of the pancreas[9,11].

Although surgical resection of the body/tail of the pancreas, achieved by an open or minimally invasive approach, is considered a less demanding operation, few evidence-based studies are available, and many issues remain unresolved. The main problems are represented by the development of postoperative pancreatic fistula (POPF) and management of the spleen (splenectomy *vs* preservation)[8,12,13].

The principal aim of this review was to investigate the ongoing surgical approaches to DP, with a special focus on minimally invasive techniques, spleen preservation and extended resections with vascular reconstruction. Endoscopic, percutaneous maneuvers and other nonsurgical maneuvers did not represent the purposes of this article and are not explained.

A web-based search of MEDLINE (accessed through PubMed and Ovid) and Cochrane databases was performed until October 2022. Many cross-matched manual references were also included. Randomized controlled clinical trials (RCTs) or meta-analyses were considered a priority. Data arising from more recent, English-written, multicentric, international studies and those with long-term follow-up and oncologic results were also considered of major interest and included in the study.

The review examines the state of the art in distal pancreatectomies, with a special focus on minimally invasive approaches and oncological-directed techniques.

CURRENT TECHNIQUES OF DP

The operation could be defined as resection of the body-tail of the pancreas (with or without concomitant splenectomy). Globally, it includes more than 20% of all pancreatic resections[14]. The first DP was reported by Lillemoe *et al*[1], although Finney[15] and Mayo[16] collected the first case series with the description of their techniques in 1900. The surgical steps have remained unchanged for decades, and most of them are still in use.

A subcostal left transverse incision is the preferred approach, but upper midline incisions are also employed. After careful exploration, the surgeon begins by accessing the retrocavity by sectioning the greater omentum, cutting some short gastric vessels to increase the surgical view and expose the anterior surface of the pancreas. The celiac axis is then identified and dissected, and the splenic artery is transected. The pancreatic neck is gently detached from the portomesenteric confluence using a finger

or blunt forceps.

The next step includes complete distal pancreatic detachment, securing each vessel originating from the splenic vein or maintaining some short gastric vessel, in the case of spleen preservation, while splenic mobilization could be achieved from left parietal ligaments in the case of concomitant splenectomy. The splenic vein should be transected distal from the inferior mesenteric vein confluence. The pancreatic neck is then transected with a selective ductal closure, and the specimen is removed. Some upgrades include vessel and/or pancreatic transection with a linear stapler, the use of a harmonic scalpel, and the employment of surgical clips[17,18].

Conventionally, DP and splenectomy have been performed to treat pancreatic cancer of the body and tail in a left-to-right retrograde fashion, in which mobilization of the spleen and pancreas is followed by vascular control and division of the pancreas[19].

After its first introduction in clinical practice, DP has substantially remained unmodified for 100 years [20,21]. In recent decades, some steps forward have been made to overcome some limits of DP and to obtain better oncological results. The most influential advances are presented below.

RADICAL ANTEGRADE MODULAR PANCREATO-SPLENECTOMY

Recently, the routes of lymphatic drainage have been investigated deeply to minimize the risk factors for margin positivity and to enhance survival after DP. The acronym Radical antegrade modular pancreatosplenectomy (RAMPS) was introduced by Strasberg *et al*[20] to address some of these important issues. His technique had the goal of achieving systematic and radical surgical dissection during DP, leading to maximum rates of negative resection margins and complete regional lymph node dissection [19].

From a technical perspective, RAMPS is a "no-touch" isolation approach to control major blood vessels, such as the splenic, renal, and adrenal vessels, by early separation of the pancreatic neck from the pancreas to the spleen[22]. The major anatomic landmarks include the left-sided portal vein, the aorta, the celiac axis, the mesenteric artery, the left-sided borders and the left kidney vein and the diaphragm. The posterior margin varies according to the location and extension of the pancreatic tumor, introducing some different subclassifications of the proper "RAMPS"[23]. In detail, anterior RAMPS includes the dissection of Gerota's fascia, the prerenal fat on the surface of the adrenal gland and the upper half of the kidney, while so-called posterior RAMPS involves the asportation of the left adrenal gland and the retroperitoneal fat tissue, with the muscle layer of the posterior abdominal wall limiting the surgical field[24].

The first published experiences reported a negative resection margin rate of up to 90%[20], although the influence of asymptomatic recurrence-free survival on overall survival remains controversial[25,26]. The systematic adoption of the RAMPS procedure has been increasing, particularly in Japan and Korea [4]. The number of patients eligible for RAMPS is small, and only recently have some prospective randomized trials of RAMPS *vs* the standard procedure been started[4,27,28]. These studies are still enrolling patients, and no definitive results are available yet. Consequently, the evidence is largely based on prospective, not randomized, studies.

Interestingly, compared to standard retrograde pancreato-splenectomy (SRPS), RAMPS has been demonstrated to reduce intraoperative bleeding[29,30] and increase R0 resection rates[4,29,30], the number of lymph nodes harvested[4,29,30] and the local recurrence rate (23.6% *vs* 49.6%; $P = 0.019$)[31], but no statistically significant difference has been found in terms of overall survival and disease-free survival[4,32]. Nevertheless, in the most recent systematic literature reviews and meta-analyses, the evidence tended to favor RAMPS in terms of safety and effectiveness (including both outcomes and overall survival)[29,33-35] with respect to SRPS, while another recent meta-analytic study suggested that RAMPS may have little effect on disease-free survival and overall survival[19].

DP WITH CELIAC AXIS RESECTION

Locally advanced disease is present in up to 40%[36,37] of patients affected by pancreatic cancer, with a median survival reported between 6 mo to 24 mo, and the longer survival time was obtained after a somewhat systematic approach[38]. However, the surgeon may also help to obtain a more radical procedure, achieving negative margins at the price of higher complication rates. A clear benefit of more aggressive surgery has not yet been proven, and the best management is driven by the application of standardized, recognized, international guidelines that propose a chemotherapy or radio-chemotherapy approach for locally advanced cancers[39,40]. More frequently, patients undergo chemotherapy plus radiotherapy to obtain regression, with reported conversion rates (unresectable to resectable) of 33%-50% and R0 resection rates comparable to standard resections[41-44].

Based on these assumptions, demolitive surgeries, such as DP with celiac axis resection (DP-CAR), have become a therapeutic option in recent decades[45]. Nimura *et al*[46] introduced a formal DP-CAR as a modified gastric-sparing approach of the Appleby procedure[47]. It consists of concomitant DP and

celiac axis resection, with the perfusion of the liver and stomach guaranteed by retrograde flow *via* the superior mesenteric artery, pancreatoduodenal arcades, and the gastroduodenal artery[48].

If venous infiltration is no longer an absolute contraindication to surgery, arterial infiltration is considered an unresectability criterion, both for technical challenges and for poor prognosis[49]. The so-called "artery-first" approach is useful as an initial surgical step to clarify arterial infiltration along the superior mesenteric artery[49]. Nevertheless, some selected patients could benefit from arterial resection if R0 margins could be obtained, with a median overall survival comparable to that of patients with localized pancreatic cancer[45,47,48,50-53]. Unfortunately, such radical surgery has high rates of morbidity (50%-80%) and mortality (3.5%-17.0%), mostly related to the liver[54] and gastric ischemia[55, 56].

A systematic review by Klompmaker *et al*[48] collected the results of 19 retrospective studies published between 1975 and 2014, including a total of 240 patients. Radical resection was obtained in 75% of patients, with 27% of patients who experienced complications, with a median overall survival of 14.4[9-48] mo. Although these results were highly flawed because the percentages of neoadjuvant chemotherapy administered differed, the sample size was small, and the enrollment period was long, the conclusion is that a subgroup of patients could benefit from by this approach[47].

Interestingly, the introduction of the FOLFIRINOX chemotherapeutic schedule (folic acid, fluorouracil, irinotecan, oxaliplatin) has enhanced the neoadjuvant approach with a more aggressive approach[57,58], leading to a higher rate of resection, clear margins and significantly better survival [59]. The assumptions imply that some older surgical experiences, including aggressive vascular resections (such as DP-CAR), could have obtained suboptimal results[47].

Klompmaker *et al*[48] reported the results of an international multicenter (20 high-volume pancreatic centers) study, including a total of 68 patients with exocrine pancreatic cancer treated from 2000 to 2016. Half of them received neoadjuvant radiochemotherapy, with more than half resulting in clear margins. Additional results from this study included the following: A 25% rate of POPF, 17 d of hospital stay, and a 90-d mortality of 16%. The median overall survival was 18 mo. The authors concluded that DP-CAR offers a survival benefit in selected patients with otherwise unresectable pancreatic cancer treated by highly skilled surgical teams working at high-volume centers[47]. The best results were achieved by combining DP-CAR with chemotherapy.

Interestingly, some pioneering experiences introduced the application of the robotic platform to overcome some of the technical limitations of laparoscopic vascular resections during pancreatic surgery (Robotic DP-CAR)[47].

One of the largest reviews comparing DP-CAR and traditional DP was published by Nigri *et al*[45]. A total of 24 articles, including 1077 patients who were divided into two groups, showed a higher percentage of T4 tumors in the DP-CAR group. Perioperative outcomes were similar in terms of POPF, complications and mortality. Patients treated with DP-CAR were more likely to have positive resection margins but less likely to receive adjuvant treatments. The overall survival at one year was similar in the two groups[45]. The authors concluded that celiac axis involvement should no longer be considered a strict contraindication to surgery in patients with locally advanced pancreatic adenocarcinoma. However, a direct comparison of DP-CAR and palliative approaches should be more informative, together with a somewhat randomized design or propensity score matching. Liu *et al*[60] reported the results of a very accurate systematic review, including 11 high-quality studies and 1072 patients, concluding that DP-CAR has worse efficacy and prognosis and is more dangerous than standard DP, but it can improve survival and quality of life than palliative treatment.

Future studies should also investigate the extent of surgical volumes and the enhanced median survival in comparison to upfront resectable pancreatic cancer.

LAPAROSCOPIC DP

The first laparoscopic DP (LDP) was performed by Gagner *et al*[61] in the mid-nineties. Since then, laparoscopy has been widely demonstrated to reduce pain, decrease blood loss, shorten hospital stay, enhance the postoperative course, provide better cosmesis and reduce costs in many abdominal procedures[62-64]. Laparoscopic techniques have also been progressively applied in DP at the price of increased cost[64,65] and with less enthusiasm because of the position and anatomical relations with major vessels[66] when compared to open surgery. Currently, LDP has been progressively becoming the preferred approach in most centers[11].

The indications for LDP are the same as those for open DP[67-69], including benign, borderline, or malignant tumors, pancreatic injury and chronic or acute pancreatitis with pseudocysts located in the pancreatic body and tail. The invasion of the surrounding organs, vascular involvement, the presence of distant spread in cancer, or acute pancreatitis are current contraindications to a robotic approach in most centers. The minimally invasive approach should be considered more challenging in a morbidly obese patient, although skilled surgeons have reported opposite conclusions[70].

The main steps of the surgical technique are similar to those of open surgery, but no formal clear standardization of the technique has been published[71,72]. The patients are usually approached in the

supine positions and tilted on the left side, and a minimum of 4 trocars are employed. Intraoperative ultrasound is recommended to identify the location of the lesion. After gentle pancreatic mobilization, the splenic vessels are identified and secured by a stapler, clips, or ligation. The pancreas is then transected using a stapler or energy device (in this case, selective duct closure is mandatory)[71].

Unfortunately, most evidence is derived from retrospective experiences, and few randomized studies have compared the minimally invasive technique with the open technique, demonstrating the superiority of MIDP in terms of reduced delayed gastric emptying, quality of life, functional recovery, reduced hospital stay, and costs[73,74]. A Cochrane review published in 2016 collected data from 12 non-RCT retrospective studies, including 1576 participants (394 LDP). No clear evidence has been reported between the two approaches in terms of short- to long-term morality and severe complications [11]. Similar conclusions were driven by the Application of the International Study Group on Pancreatic Fistula (2017) criteria, with LDP having surgical outcomes comparable with those of open DP (ODP). However, LDP resulted in lower blood loss, fewer complications, and shorter hospital stay[75].

Interestingly, LDP is underused in clinical practice[76], while ODP is still considered the standard procedure by most surgeons, including the publication of widely recognized benchmarks[77]. Despite the scarce evidence available, the application rate of LDP varied over time and differed between countries. Data extracted from nationwide database analysis reported the application of LDP in 26% of cases between 1998-2009 in the United States[78], and this rate did not exceed 10% from 2005-2013 in the Netherlands[79]. Moreover, a more recent publication from the Norwegian Patient Register reported a laparoscopic approach in 59% of DP procedures between 2012 and 2016[80].

A possible explanation of these risks could be related to the concentration of casistic in few specialized centers, which offer the maximum expertise in pancreatic pathology and highly expensive updated instrumentation. Specific participation in the training course could improve both the use and outcomes of LDP, while the initial introduction of the technique implies careful patient selection[81]. The learning curve to gain sufficient skills is reported to range between 11 and 40 procedures[81-84], and the lack of reconstructive time contributed to feeling that LDP was much more feasible than laparoscopic duodenopancreatectomy[65]. Interestingly, some authors reported similar operative times with respect to open procedures, considering it a surrogate parameter of proficiency[85,86].

Nevertheless, another possible limitation to the widespread application of LDP is the cost-effectiveness, although the balance remains difficult to evaluate due to the variability of health systems between countries and the different costs of disposable surgical devices[86]. The supposed gain in terms of the reduced hospitalization, incidence of complications, and reduction of days off-work are often misinterpreted if not available in many publications.

In 2020, an international panel of expert surgeons published guidelines for the application of minimally invasive techniques to pancreatic surgery in an attempt to overcome the uncertainties about this issue in terms of benefits and applicability and to standardize most of the indications[9,73].

The risk of POPF is the major impacting complication after open and laparoscopic DP and is highly related to prolonged intra-abdominal drainage, hemorrhage, readmissions, sepsis and certainly mortality[87,88]. Older studies reported a higher rate (39%) of POPF after minimally invasive DP compared to open DP[89], but others failed to find significant differences after careful statistical patient stratification and homogenization[90]. Moreover, in 2021, a new POPF risk score (ua-FRS) was validated for minimally invasive pancreatic surgery[91], with a reported global incidence rate of 21%. A careful surgical technique, independent of the approach (open or minimally invasive), is the best option to minimize the risk of POPF[91]. Many different approaches (some comparative) to pancreatic transection have been published, including scalpel, electrocautery, ultrasonic/harmonic, and laparoscopic staplers [92-97], but no evidence is available to support one method over another, and most evidence is derived from ODP studies. The use of fibrin sealants and similar products has little effect on POPF in people undergoing DP[96,97].

Many researchers hypothesize some advantages of MIS in decreasing the proinflammatory and immunologic response to surgical trauma[98,99] that is associated with a superior oncologic result, while a robust meta-analysis demonstrated that LDP might be safer with regard to the oncological outcomes of pancreatic ductal adenocarcinoma patients[100]. A study by Shin *et al*[101] specifically compared LDP and ODP in 150 cancerous patients, with oncologic adequacy considered the primary endpoint. The authors reported a 5-year survival rate, the length of surgery, the number of harvested lymph nodes, the resection margin status, and the incidence of POPF to be similar between the two groups.

Spleen preservation is considered to be mandatory for patients operated on for IPMN or less aggressive neuroendocrine tumors located in the pancreatic body and tail, leading to a reduction in both blood loss and postoperative complications[102-108]. Warshaw[109] described a technique in which splenic vessels are ligated with the preservation of the short gastric and left gastroepiploic vessels, while Kimura spared the splenic vessels by careful detachment of pancreatic vessels from the major trunks [110]. Although this concept has recently been discussed, the two available spleen-preservation techniques[111,112] are feasible by laparoscopy in the hands of experienced surgeons[111]. Most published papers reported similar rates of spleen preservation[103,105,106].

Table 1 State of the art of distal pancreatectomy and future directions

Planned operation	To be considered	Present	Ongoing research	To be matched with
DP	Age, comorbidities	Laparoscopic	Robotic	Laparoscopy
DP + splenectomy	Age, comorbidities, cancer, local anatomy	Laparoscopic	Robotic	Laparoscopy
RAMPS	Age, comorbidities, cancer	Laparoscopic, open	Robotic	Open surgery
DP-CAR	Age, comorbidities, cancer	Open	Laparoscopic, robotic	Open surgery

DP: Distal pancreatectomy; RAMPS: Radical proximal-distal modular pancreatosplenectomy; DP-CAR: Distal pancreatectomy with celiac axis resection.

ROBOTIC DP

The recent, widespread introduction of the da Vinci® Surgical Systems (Intuitive Surgical, Inc., Sunnyvale, CA, United States) robot has led many surgeons to address pancreatic disease with this technology[113]. If minimally invasive pancreaticoduodenectomy (laparoscopic, hybrid, or robotic) is far from routinely adopted in the community, robotic-assisted distal pancreatic resection (RDP) should potentially resolve many of the major issues of pure laparoscopy, including the preservation of the spleen[114]. For example, few retrospective series have reported the percentages of the spleen left in situ (when indicated) in up to 90% of cases[115,116], while neither the traditional open nor laparoscopic approach has been reported to reach 90%[117]. In addition, robotic articulated stable instrumentation could help the surgeon improve tissue dissection and lymphadenectomy when treating pancreatic cancer[118-120]. Nevertheless, definitive data on the robotic approach are still needed.

A meta-analysis by Zhang *et al*[121], which included seven trials, examined 137 robotic and 203 open pancreatectomies. Many of the analyzed parameters, such as morbidity, blood loss and length of hospital stay, favored robotic procedures, but none of the differences reached statistical significance. The incidence of POPF was similar.

Another more recent meta-analysis by Feng *et al*[122] reported better results of RDP compared to LDP in terms of operative time, tumor size, and lymph node dissection, with a higher R0 resection rate ($P < 0.0001$)[122]. Other meta-analyses comparing RDP and LDP reported the former as safe and feasible, with a low rate of conversion to open surgery, blood loss, a shorter length of stay and an increased rate of spleen preservation[117,123]. However, demographic discrepancies, underpowered RDP samples and differences in oncological burden do not permit certain conclusions regarding the oncological safety of RDP and LDP for pancreatic adenocarcinoma[123]. The oncological safety of robotic DP compared to LDP has been demonstrated[2] in a national database and is currently being evaluated in a multicenter European randomized trial (DIPLOMA trial)[124].

In conclusion, robotic DP is a safe and feasible procedure with perioperative and oncological outcomes comparable to those of LDP and open traditional surgery. Many technical advantages seem to permit the surgeon to overcome many of the drawbacks of pure laparoscopy, including a steep learning curve, complex dissection and ergonomic issues, maintaining the same advantages of a minimally invasive procedure (reduced blood loss, shorter hospitalization and improved cosmetic results)[113]. Costs and availability remain the main limitations of the robotic approach[125] (Table 1).

CONCLUSION

Surgical resection has the best chance to cure pancreatic disease, including malignancy, precancerous lesions, and inflammatory involvement. Nevertheless, pancreatic surgery has high morbidity and mortality rates and is especially challenging for surgeons operating on elderly surgical patients. Therefore, the purpose of ongoing research and surgical efforts is to reduce the impact of surgical trauma through minimally invasive approaches, spleen preservation when indicated, and maintaining and improving the accuracy of oncologic dissection (*i.e.*, clear margins and proper lymphadenectomy). All the issues mentioned above can be addressed by laparoscopic and robotic surgeries, which have been well established for distal pancreatic resections. However, such procedures require excellent surgical skill, training experience with proctors, and case-load concentration in high-volume hospitals with the best resources. In conclusion, if DP with or without a radical approach, vascular resection or splenectomy is thought to be easier than cephalic resection, it should not be considered easy in every case.

FOOTNOTES

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