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TOPIC HIGHLIGHT

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Laparoscopic distal pancreatectomy: Up-to-date and literature review

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Abstract

Pancreatic surgery represents one of the most challenging areas in digestive surgery. In recent years, an increasing number of laparoscopic pancreatic procedures have been performed and laparoscopic distal pancreatectomy (LDP) has gained world-wide acceptance because it does not require anastomosis or other reconstruction. To date, English literature reports more than 300 papers focusing on LDP, but only 6% included more than 30 patients. Literature review confirms that LDP is a feasible and safe procedure in patients with benign or low grade malignancies. Decreased blood loss and morbidity, early recovery and shorter hospital stay may be the main advantages. Several concerns still exist for laparoscopic pancreatic adenocarcinoma excision. The individual surgeon determines the technical conduction of LDP, with or without spleen preservation; currently robotic pancreatic surgery has gained diffusion. Additional researches are necessary to determine the best technique to improve the procedure results.

Key words: Pancreas resection; Laparoscopic distal pancreatectomy; Left pancreatectomy; Open pancreatectomy; Pancreatic fistula; Splenectomy; Spleen-preserving technique

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PANCREATIC SURGERY AND LAPAROSCOPY

Pancreatic surgery represents one of the most challenging areas in digestive surgery, and it has been historically associated with up to 50% morbidity and 5% mortality[1,2]. It is usually performed by open approaches, but following the increased experience in laparoscopic surgery of other districts and the availability of new technological devices, an increasing number of laparoscopic pancreatic procedures has been performed[3,4].

Laparoscopy has initially been used only for staging

pancreatic cancer. Cuschieri reported the first description of laparoscopic pancreatic resection in 1994[5]; few years later, Gagner published his initial experience with laparoscopic distal pancreatectomy (LDP) with spleen preservation including eight cases[6]. Actually, LDP has gained world-wide acceptance because the procedure does not require anastomosis or other reconstruction[7,8].

A comparison between open surgery and LDP confirms advantages commonly ascribed to minimal-access surgery such as reduced postoperative pain, faster recovery, fewer wound related and general morbidity[9-19]. Although the laparoscopic approach to distal pancreatectomy has become a feasible option over the last few years, it still faces two problems: firstly, sparing the spleen with or without ligation of the splenic vessels, and secondly, controlling the leak from the pancreatic remnant and pancreatic fistula[20]. However, some controversy about its indications and safety concerning long-term oncologic outcome, still exist[21-23].

Literature concerning LDP is relatively poor: Case reports, small case series and few multicentric larger studies have been published[21,24-26]. The aim of this paper is to review the most recent literature, in order to offer an up-to-date concerning the indications, the results and some technical controversial issues concerning LDP.

LAPAROSCOPIC DISTAL PANCREATECTOMY: LITERATURE REVIEW

A web search, focusing on humans, was performed by PubMed database, including papers published in the English language up to 20 November 2011, using the key words "laparoscopic distal pancreatectomy" or "left-side pancreatectomy". A total of 388 papers were found. The bibliographic research was further expanded considering the related references cited by the above-mentioned papers.

In order to avoid the confounding effect of case reports and small series, a more refined research, including series of at least 30 cases, was performed. Results published only in the abstract form were excluded; in case of multiple publications from the same authors or institutions, only the latest and largest series were considered, in order to avoid the duplication of cases.

Twenty-two papers, including 2016 operated patients were found when literature search was reviewed. The median number of cases included were 70 (range: 30-359). The results are summarized in the Table 1. Eighteen papers included retrospective series; patients were prospectively included only in four studies. Eight papers derived from multicentre group studies.

The review of the literature confirms that LDP may be considered a feasible and safe technique[21,27,28]. It represents more than 70% of the laparoscopic pancreatic resections actually performed[29]. However, the major part of the studies on LDP is represented by case series with a relatively small number of patients[23,30]; only 6% of papers includes more than 20 cases. Most of the studies have a retrospective design; subsequently, it is still difficult to trace any conclusion from the results of these experiences because of the insufficient level of evidence.

Several comparative studies have shown that the average operative time, blood loss, morbidity, mortality and length of hospital stay after laparoscopic access might favourably comparable with those after open surgery[9,11-19,29].

In particular Mehta *et al*[17] describes a tendency toward a shorter duration of surgery in laparoscopic resection compared to open, although without a significance level ($P = 0.071$).

By contrast, with these optimistic prospects, Baker has published a single-institution comparison between laparoscopic and open distal pancreatectomy, focusing on post-discharge readmission. The laparoscopic approach has been associated with a shorter hospital stay, but a higher rate of late readmission requiring interventional procedures[31]. Furthermore, LDP cannot be considered a routine laparoscopic procedure, since it requires an advanced technical laparoscopic skill.

To date, several aspects are still controversial, mainly related to the indications, the results of the procedure and some technical details.

INDICATIONS TO LAPAROSCOPIC DISTAL PANCREATECTOMY

The indications for LDP vary, depending on the study, although most operations of LDP have been performed because of benign lesions, neuroendocrine tumors or low-grade malignancies (in particular cystic tumors)[29,32]. However some cases of pancreatic adenocarcinoma have been reported[33]; the results of laparoscopic resection for left pancreatic adenocarcinoma are limited, and its safety for long-term oncologic outcome is strongly debated. This approach for the treatment of pancreatic carcinoma still requires prospective validation[34] (Table 2).

LDP has also been performed in patients with chronic pancreatitis[35]; laparoscopic necrosectomy for acute necrotizing pancreatitis has been also described[36]. Steering wheel injury typically involves pancreatic parenchyma in front of the vertebra; LDP preferably with spleen preservation, has been indicated for patients with pancreatic trauma[37-39].

Persistent hyperinsulinemic hypoglycemia of infancy is a rare disease due to focal islet cell adenomatosis that may cause severe neurogenic damage. LDP or enucleation of the focal lesion has been performed in pediatric patients, while an open near-total pancreatectomy has been indicated in an infant with sustained hypoglycemia[40,41].

Surgery is the only curative modality currently available for resectable pancreatic neuroendocrine tumors[26,42]. Spleen-preserving LDP is feasible and can be achieved in

Table 1 Laparoscopic distal pancreatectomy: Results of the literature review

Ref.	Year	Study type	*n*	Pathology
Butturini *et al*[98]	2011	Retrospective	43	SCN (14), MCN (9), SPT (4), NET (9), other (7)
Mekeel *et al*[99]	2011	Retrospective	34	SCN (11), NET (8), IPMN (6), MCN (4), other (5)
Nakamura *et al*[100]	2011	Retrospective	47	NET (9), MCN (10), IPMN (6), SPT (5), P (6), other (11)
Mehta *et al*[17]	2011	Prospective	30	NET (12), IPMN (4), ADK (7), other (7)
Song *et al*[101]	2011	Retrospective	359	SCN (51), MCN (72), SPT (52), NET (36), IPMN (76), ductal ADK (24), P (25), cyst (13), others (10)
Zerbi *et al*[102]	2011	Prospective	95	NET
Røsok *et al*[103]	2010	Retrospective	117	NET (53), carcinoma (28), metastases (5), cystic tumours (48), other (37)
Vijan *et al*[12]	2010	Retrospective	100	Cystic benign neoplasm (49), solid benign neoplasm (27), malignant neoplasm (20), other (4)
Jayaraman *et al*[104]	2010	Retrospective	107	NA
DiNorcia *et al*[16]	2010	Retrospective	95	NA
Ziegler *et al*[105]	2010	Retrospective	126	NA
Giulianotti *et al*[80]	2010	Retrospective	46	ADK (6), NET (carcinoma) (5), benign neoplasm (28), other (6)
Finan *et al*[13]	2009	Retrospective	50	ADK (6), MCN (9), SCA (9), IPMN (4), NET (9), other (13)
Weber *et al*[106]	2009	Retrospective	219	MCN (45), SCN (29), IPMN (23), cyst (14), SPT (5), NET (45), ADK (16), metastases (9), P (14), other (19)
Yoon *et al*[107]	2009	Retrospective	35	SPT (7), IPMN (4), MCN (4), NET (4), other (16)
Kooby *et al*[27]	2008	Retrospective	159	Cystic neoplasm (85), solid neoplasm (60), P (14), benign neoplasm (102), ADK (16)
Taylor *et al*[108]	2008	Retrospective	46	SCN (10), ductal ADK (9), MCN (6), other (19)
Laxa *et al*[109]	2008	Retrospective	32	SCN (10), NET (6), mucinous neoplasm (4), IPMN (4), other (8)
Sa Cunha *et al*[7]	2008	Prospective	37	NA
Melotti *et al*[110]	2007	Prospective	58	MCN (19), SCN (13), NET (9), SPT (5), ductal ADK (5), other (7)
Fernández-Cruz *et al*[28]	2007	Retrospective	82	Inflammatory tumor (8), cystic neoplasm (29), IPMN (10), NET (22), ductal ADK (13)
Mabrut *et al*[21]	2005	Retrospective	99	NA

n: Number of patients; SCN: Serous cystic neoplasm; MCN: Mucinous cystic neoplasm; ADK: Adenocarcinoma; SPT: Solid pseudopapillary tumor; IPMN: Intraductal papillary mucinous neoplasm; NA: Not available; NET: Neuroendocrine tumor; P: Pancreatitis. Number of case for each pathology are report between parenthesis.

Table 2 Indications to laparoscopic distal pancreatectomy

Benign disease	Borderline disease	Malignant disease
Acute/chronic pancreatitis	Neuroendocrine tumor	Invasive carcinoma
Trauma	Mucinous cystic neoplasm	Metastatic renal cell carcinoma
Persistent hyperinsulinemic hypoglycemia of infancy	Intraductal papillary mucinous neoplasm	
Serous cystic neoplasms		
Transplantation in the living donor		

most cases; it is indicated for insulinomas of the pancreatic body and tail. Intraoperative laparoscopic ultrasonography is essential to localize the tumor and to evaluate the gland for additional tumors. If the insulinoma is benign, solitary, and not close to the main duct, a laparoscopic enucleation of the neoplasm may be indicated[25,43,44].

Laparoscopic resections have been also performed in some patients with gastrinoma, VIPoma, glucagonoma[45], pancreatic polypeptidoma[46], or other islet neoplasms including so-called non-functioning tumors[6]. However, some of these neuroendocrine neoplasms are often malignant and conversion to open surgery is necessary in cases of gastrinomas and VIPomas complicated by lymph node metastasis[6,47,48].

In case of potentially malignant neuroendocrine neoplasms in the pancreatic body/tail, LDP might be indicated, but laparoscopic en bloc splenectomy with resection of the spleen vessels and regional lymph-nodes dissection are recommended[4]. In case of multiple endocrine neoplasia-1 (MEN-1) patients, multiple neoplasms are common (especially gastrinomas); in these cases tumors are also located at gastroduodenal sites; the intraoperative localization of the tumors by laparoscopic approach, is not always possible even by the laparoscopic ultrasound; subsequently it is not usually indicated[48]. Furthermore, since a prolonged postoperative follow-up (at least 10 years) is required in case of potentially malignant neuroendocrine tumors, consistent data concerning the cure and recurrences rate, are still not available.

Pancreatic mucinous cystic neoplasm (MCN) represents a further possible indication to LDP. It groups a spectrum of lesions ranging from benign mucinous cystadenoma to mucinous cystadenocarcinoma. MCN is characterized by a distinct ovarian type stroma; patients with these lesions are usually relatively young women, with the peak around in the fifth decade of life. These neoplasms are more common in the body/tail of pancreas and a complete resection of the lesion is indicated. In patients with MCN several authors[49,50] have reported successful treatments by LDP.

The pancreatic serous cystic neoplasms are usually benign cystic neoplasms. When serous cystic neoplasms are symptomatic or when a differential diagnosis from potentially malignant cystic neoplasm is not possible,

a resection (possibly LDP) is indicated[49-52]. In a large comparative study between open and LDP, cystic lesions represented 59% of the laparoscopically resected tumors and 46% of the tumor excised by a laparotomic approach[19].

Intraductal papillary mucinous neoplasms (IPMN), non-invasive mucin-producing, predominantly papillary, or rarely flat epithelial neoplasms arising from the main pancreatic duct (MD-IPMN) or its secondary branches (BD-IPMN), are grossly visible[53]. They involve the head of the pancreas more commonly than the body/tail and they affect older patients with the peak age in the seventh decade. For IPMN in the body/tail of the pancreas, LDP has been performed, but one should be aware that some IPMN is associated with invasive carcinoma, as it is for MCN[53,54].

LDP has also been carried out in patients with pancreatic invasive carcinoma[23], although the questions about the oncological consequences of laparoscopic pancreatic surgery remain strongly controversial[21].

The positive margin resection rate in pancreatectomy for ductal adenocarcinoma is difficult to understand because there is no defined standard for histologic margin assessment. A recent review of the large randomized trials highlight that positive margin rates ranged from 0% to 83%[55].

A prospective observational study comparing open *vs* LDP has shown that the number of lymph nodes removed during the laparoscopic procedure was significantly inferior in comparison to the open approach[10]. Another recent analysis from a multicentre group, has compared the results of laparoscopic and open distal pancreatectomy applied to pancreatic ductal carcinoma. Cancer outcomes in short-term (lymph nodes harvest and margin status) and long-term (survival) were found to be similar in both groups[32,33]. Finally, LDP have been sporadically described also for metastatic renal cell carcinoma[56] and for pancreas transplantation in the living donors[57,58].

SURGICAL TECHNIQUES

The individual surgeon determines the technical conduction of LDP; it is usually performed in a supine or in a right lateral position[59]. However, several technical variants may be used, and some controversies still exist. The main controversial aspects in LDP are related to the preservation of the spleen, by the number and location of orifices needed for approaching the pancreas, the extent of the resection and the technique used for the parenchymal transection.

Traditionally, distal pancreatectomy has been performed with splenectomy. However the spleen plays an important role in the immune system and spleen-preserving distal pancreatectomy is preferable, in patients with benign diseases or non-invasive neoplasms[8,21,51,60].

The rate of splenic conservation of LDP is reported to be between 32% and 84%[14,17,42]. Some comparative studies have assessed the outcomes preoperative intent of splenic conservation in distal pancreatectomies performed by laparoscopic and open approaches, with a higher success rate of preservation in the first group[14,17]. This is surely due to the better vision afforded by the magnification, used in laparoscopy.

Preservation of the spleen with distal pancreatectomy can be undertaken either with preservation or with sectioning of the splenic vessels by maintaining the blood flow to the spleen *via* short gastric vessels (technique of Warshaw[61]). The latter method is associated with a shorter operation time, less blood loss, and a shorter hospitalization. The subsequent appearance of gastric varices is a consequence of loss of the splenic vein but no bleeding from these collaterals during long-term follow up, has been described. However, a splenic infarction after the laparoscopic procedure of Warshaw[62] has been documented in several case reports[63].

A technical difficulty during the preservation of splenic vessels is the division of numerous shorts tributaries from the splenic vein spreading toward the pancreatic body/tail, that requires special caution[64]. The appropriate usage of modern technologies (electro thermal bipolar vessel sealer, ultrasonic coagulating shears) can achieve secure haemostasis of tributaries from splenic vessels.

The hand-assisted laparoscopic surgical techniques have been utilized in LDP, in order to facilitate the splenic vessel preservation, because incidental bleeding can be immediately stopped by finger compression, and in large cystic tumors for a safe mobilization of the tumor and adjacent tissue. Hand ports for the insertion of operator's left hand are placed through an upper midline incision, right subcostal incision, or right lower-quadrant transverse incision according to the preference of surgeons[65-68].

Single incision laparoscopic surgery has gained attention for its minimal invasiveness and aesthetic results. This approach has been commonly described for cholecystectomy and appendectomy[69-71]; recently it has also been reported for LDP[72]. It may be effective as conventional laparoscopic pancreatectomy, when performed by expert hands although it is still a challenging procedure[58]. Further studies are necessary to determine the advantages of this procedure in comparison with standard laparoscopy.

Even though laparoscopic surgery of the pancreas remains a very challenging technique, the classically available instruments have some relevant limits. Today, following the increasing use of the robotic surgery in other fields of general surgery, some robot-assisted pancreatic resections have been reported[73-75]. Robotic surgery, can bridge the gap between minimally invasive surgery and complex pancreatic surgery, thus extending the indications for minimally invasive pancreatic surgery.

Robot-assisted surgery increases the degrees of freedom of forceps manipulation and yields three-dimensional images[22,73,76-79]. It is a procedure with some technical

and oncological advantages over other minimally invasive techniques for distal pancreatic tumors, due to the stability of the operative field, the 3D, magnified vision, and the articulated robotic arms. Moreover, the robotic articulated arms permit a superior handling of vascular structures and articulated instruments minimizing manipulation of the pancreatic gland. This technique minimizes the risk of pancreatic capsule rupture as well as tumor cell dissemination, respecting oncological surgical standards and it could provide an increased chance for spleen preservation. Giulianotti *et al*[80] has highlighted that robot-assisted laparoscopic pancreatic surgery achieves complication and mortality rates comparable to open surgery approaches, but offers the advantages of minimally invasive surgery. However, robotic surgery has high costs especially concerning the installation and the operation time, which is longer than open surgery; at the same time, it also needs an adequate learning curve.

The extent of a resection in LDP is another controversial topic. It varies depending on the pathology. For example, when a non-invasive MCN is located in the tail of the pancreas, the gland can be divided to the right of the cystic lesion with a minimal margin and only the tail of the pancreas removed. For chronic pancreatitis, it is typically divided at the pancreatic neck anterior to the superior mesenteric vein[4,35]. Recently, pancreatic surgeons have performed parenchyma-sparing resections more frequently in order to decrease the rate of postoperative pancreatic insufficiency. Oncological radicality is essential and extended resections may be necessary in the setting of IPMNs, which encompass a spectrum of lesions from adenoma to invasive carcinoma.

Intraoperative examination of the transection margin is of paramount importance in the management of MD-IPMNs[81-83]. The International Association of Pancreatology guidelines for the management of IPMNs suggest that when adenoma or low-grade pancreatic intraepithelial neoplasia is found intraoperatively in a resection margin, no further resection is needed. In case of borderline neoplasms, high-grade dysplasia or invasive carcinoma, an extension of the surgical resection to a negative margin, requires total pancreatectomy[53].

MORBIDITY

The most frequent complications after distal pancreatectomy are the fistula formation and collection[21,84,85]; they are usually related to pancreatic parenchymal transection techniques, that is another controversial topic.

In 2005 the International Study Group on Pancreatic Fistula Definition consensus paper defined a postoperative pancreatic fistula as the existence of any fluid output after postoperative day three with amylase content greater than three times the upper normal serum value[86].

Mabrut reviewed a total of 897 patients who underwent open distal pancreatectomy and reported the incidence of pancreatic fistula to be 3.5%-26% (average 13%)[21]. The incidence of pancreatic fistula with laparoscopy in studies that involved at least ten patients ranged from 0% to 27%[85].

Various risk factors for fistula formation have been reported after distal pancreatectomy. It is likely to occur in a pancreas with a soft texture[21,84,85,87], and when a selective identification and ligation of the main pancreatic duct has not been performed[87-89].

Some authors have suggested that the selective ligation may be more difficult during laparoscopy and may contribute to increased fistula rates[21]. Nevertheless, comparative studies showed that the laparoscopic approach results in a similar rate of fistula formation than the open approach[14,15,17]. A meta-analysis of studies comparing minimally invasive (laparoscopic or laparoscopically assisted) to the open approach, showed a lower rate of pancreatic fistula formation for minimally invasive approach[11]. However these results need cautious interpretation, because they depend on the study by Kooby, that relied on a definition different from that of the other studies[27].

The debate regarding the technique of stump closure after distal pancreatectomy continues. All approaches, including fibrin glue, sealants, patches, stapler closure, electrocautery and suture have been tested in numerous studies[90,91].

The distal pancreatectomy trial included 352 patients that were randomly assigned to stapler or hand-sewn closure of the pancreatic remnant: both groups showed equal fistula rates of 30% and 36%[92].

The main duct ligation and parenchymal transection during LDP is most commonly performed using endoscopic linear staplers. The surgeon may oversew the staple line to ensure pancreatic ductal closure and haemostasis. In such cases, ultrasonic coagulating shears can be used, usually followed by a monofilament suture to secure the closure of the main pancreatic duct[21,63,93,94].

In a recent study, Sartori *et al*[95]describes a new technique of pancreatic transection by the electrothermal bipolar vessels sealer, which seals vessels and other tubular structures by reforming parietal collagen and elastin, particularly suitable for laparoscopic left pancreatectomy; but a possible suitability in terms of fistula reduction is still under investigation.

When using the hand assisted laparoscopic technique, the pancreas can be divided through the hand port wound as for conventional open surgery.

To prevent post-operative fistula, octreotide and its analogues, have also been used since 1990. However, despite twenty years of clinical use and performance in numerous studies, a recent Cochrane meta-analysis concluded that evidence is still lacking to give clear recommendations[96].

Intraabdominal drains are commonly used in most centres after pancreatic resections. There is no evidence that persisting drainage of postoperative wound fluid has a positive effect in avoiding fistulae; on the contrary, a recent study sustains that drains kept in situ for more than three days enhance fistula development[97].

The management of postoperative fistula remains a therapeutic challenge. Depending on patient's clinical conditions, it ranges from persisting drainage without any further measures, up to revision surgery. However in literature, after LDP, a conservative management of pancreatic fistula is usually described[85,87].

In conclusion, LDP is a feasible and safe procedure in patient with benign or low grade malignancies. Decreased blood loss and morbidity, early recovery and shorter hospital stay may be the main advantages. The introduction in particular of robotic surgery, can bridge the gap between minimally invasive surgery and complex pancreatic surgery. On the other hand, additional researches are necessary to determine the best technique for minimizing pancreatic fistula formation and to improve the results of procedure.

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