Laparoscopic versus open distal pancreatectomy for benign or premalignant pancreatic neoplasms: a two-center comparative study[*]

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Abstract: Objective: To compare the peri-operative outcomes for laparoscopic distal pancreatectomy (LDP) and open distal pancreatectomy (ODP) for benign or premalignant pancreatic neoplasms in two institutions. Methods: This prospective comparative study included 91 consecutive patients who underwent LDP (n=45) or ODP (n=46) from Jan. 2010 to Dec. 2012. Demographics, intra-operative characteristics, and post-operative outcomes were compared. Results: The median operating time in the LDP group was (158.7±38.3) min compared with (92.2±24.1) min in the ODP group (P<0.001). Patients had lower blood loss in LDP than in the ODP ((122.6±61.1) ml vs. (203.1±84.8) ml, P<0.001). The rates of splenic conservation between the LDP and ODP groups were similar (53.3% vs. 47.8%, P=0.35). All spleen-preserving distal pancreatectomies were conducted with vessel preservation. LDP also demonstrated better post-operative outcomes. The time to oral intake and normal daily activities was faster in the LDP group than in the ODP group ((1.6±0.5) d vs. (3.2±0.7) d, P<0.01; (1.8±0.4) d vs. (2.1±0.6) d, P=0.02, respectively), and the post-operative length of hospital stay in LDP was shorter than that in ODP ((7.9±3.8) d vs. (11.9±5.8) d, P=0.006). No difference in tumor size ((4.7±3.2) cm vs. (4.5±1.8) cm, P=0.77) or overall pancreatic fistula rate (15.6% vs. 19.6%, P=0.62) was found between the groups, while the overall post-operative complication rate was lower in the LDP group (26.7% vs. 47.8%, P=0.04). Conclusions: LDP is safe and effective for benign or premalignant pancreatic neoplasms, featuring lower blood loss and substantially faster recovery.

Key words: Laparoscopy, Distal pancreatic resection, Pancreatic neoplasm, Splenic preservation, Pancreatic benign tumors

1 Introduction

Application of minimally invasive techniques, i.e. laparoscopic pancreatic surgery, in the management of distal pancreatic lesions is increasing. It is particularly adapted to distal pancreatic surgery because of the absence of anastomosis in this surgery. Laparoscopic distal pancreatectomy (LDP) was first reported by Cuschieri (1994). Since then, several case series (Melotti *et al.*, 2007; Taylor *et al.*, 2008; Song *et al.*, 2011), comparative cohort studies (Mabrut *et al.*, 2005; Kooby *et al.*, 2008; Jayaraman *et al.*, 2010), and meta-analysis reports (Jusoh and Ammori, 2012; Pericleous *et al.*, 2012; Xie *et al.*, 2012; Nakamura and Nakashima, 2013) have shown that LDP provides similar advantages that have been

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demonstrated for other minimally invasive surgeries. In patients who underwent laparoscopic surgeries, there were fewer surgical site infections and complications, and decreased length of stay and expenses compared with open distal pancreatectomy (ODP) (Fox *et al.*, 2012; Kneuertz *et al.*, 2012; Venkat *et al.*, 2012).

Laparoscopy seems to be under-utilized for distal pancreas resection owing to the complexity of the procedure, the high requirement of technical skills by the surgeon in dissecting the important vascular, and the lower acceptance in the resection of malignant lesions. Further, the limitations of selection bias, small sample size, and pooling of multi-institutional data have hindered a meaningful comparative trial of LDP and ODP. Randomized, controlled trials comparing LDP with the ODP are limited. No consensus exists for or against the use of the laparoscopic approach for distal pancreatectomy in benign and malignant lesions.

To better elucidate the benefits of LDP, here we report a prospective comparative study of the two approaches at two high-volume institutions, aiming to systematically compare the peri-operative outcomes of LDP with ODP for benign or premalignant pancreatic neoplasms.

2 Materials and methods

2.1 Patients

This two-center study was performed from Jan. 2010 to Dec. 2012. Data from 91 consecutive patients who underwent distal pancreatectomy in the Department of General Surgery, Zhongshan Hospital, Shanghai Medical College, Fudan University (Shanghai, China) and the Department of General Surgery, Institute of Micro-Invasive Surgery, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University (Hangzhou, China) entered into our surgical database. This study had been approved by the ethics boards of the two hospitals, and informed consent was obtained from all patients. Patients with benign or premalignant pancreatic neoplasms were screened with thin slice computerized tomography or magnetic resonance imaging before the operation. Patients with malignant tumors, pregnant or lactating women, or those with child-bearing potential, patients who had multiple organ resections during distal pan-

createctomy or a history of abdominal surgery, were excluded.

Pre-operative variables included age, gender, body mass index (BMI), significant co-morbidity, operation history, hepatic and renal function, coagulation function, carcinoembryonic antigen, CA19-9, and α-fetoprotein. Intra-operative variables such as operative time, operative blood loss, as well as post-operative time to resume normal daily activities and first time of oral intake, were recorded. Data for post-operative complications within 30 d of the operation were gathered, such as pancreatic fistula, delayed gastric emptying, wound infections, intestinal adhesion and ileus.

The indications for surgical resection of pancreatic cystic neoplasms in our study were as follows: (1) tumor size larger than 4 cm; (2) after surveillance for rapid rate of growth; (3) presence of symptoms such as abdominal pain or distension; (4) inability to definitely exclude a premalignant or malignant tumor.

Distal pancreatectomy was defined as resection of the pancreas to the left of the portal vein, with or without splenic conservation. Pancreatic fistula and delayed gastric emptying was defined according to the guidelines of the International Study Group on Pancreatic Fistulas (ISGPF) (Bassi *et al.*, 2005; Wente *et al.*, 2007). Operative time was defined as the time between patient entry into and exit from the operation room. Post-operative diet began on the first day after first bowel gurgles. Length of stay was calculated from date of operation to date of hospital discharge. Peri-operative mortality was defined as death within 30 d of the operation or within the same hospital admission as the operation.

2.2 Surgical procedure

2.2.1 ODP

All the ODP surgeries were done by one group of surgeons in Zhongshan Hospital (Shanghai, China).

The peritoneal cavity was entered by subcostal incision. The gastrocolic ligament was divided and the omental sac opened. After careful intra-operative exploration, we proceeded to resection the pancreas. The superior and inferior borders of the pancreas were defined, and the splenic vessels were identified and preserved or ligated depending on whether splenic preservation was to be performed. The pancreas was mobilized and transected with the Endo-GIA stapler.

At the end of the operation, a drain was placed into the left subdiaphragmatic area.

Attempts were made in all patients to conserve the spleen. To avoid the occurrence of splenic infarction or splenic abscess, we used the surgical technique for splenic salvage with conservation of the splenic artery and vein, rather than ligation of the splenic pedicle with preservation of the short gastric vessels (Warshaw, 1988). A splenectomy was performed during distal pancreatectomy for the following reasons: (1) splenic infarction, thrombosis of the splenic vessels, or regional portal hypertension; (2) difficult dissection from the splenic vessels or splenic hilum; (3) intra-operative bleeding from the splenic vessels or the spleen.

2.2.2 LDP

All the LDP surgery was done by one group of surgeons in the Sir Run Run Shaw Hospital (Hangzhou, China).

The technique for LDP has been described elsewhere (Abu Hilal *et al.*, 2009). In short, five ports (three 5-mm ports and two 10/12-mm ports) were used. Typically, the first trocar—preferably optical— was inserted in the umbilicus. The remaining trocars were placed as follows: two 5-mm trocars were placed in the subcostal area in the anterior axillary line on both sides; a 12-mm trocar was placed outside the right rectus abdominis 2 cm above the umbilicus, which permits use of an Endo-GIA stapler, and a 5-mm trocar on the opposite left side. After establishing laparoscopic access, the pancreas was exposed through the division of the lesser sac. The splenic attachments and the short gastric vessels were divided. The splenic vessels were dissected from the pancreas to the splenic hilum. The pancreas was transected with the Endo-GIA stapler. When simultaneous splenectomy was being performed, the splenic artery and vein were ligated and divided.

If imaging examination before operation indicated a splenic preservation, the pancreas was dissected off

the splenic vessels; tributary vessels were treated with the harmonic scalpel or clips. Splenic vessels were all conserved during spleen-preserving pancreatectomies.

The specimen was then placed in an endoscopic bag. A minilaparotomy can be carried out at the umbilical port. Peritoneal drains were placed adjacent to the pancreatic remnant and brought out of the abdomen through the 5-mm port sites. In case of intra-operative bleeding from the splenic vessels or the spleen, a conversion from LDP to ODP was necessary.

2.3 Statistical analysis

Demographic, procedural, and post-operative data were documented. Continuous variables were reported as mean±standard error (SE). Categorical variables were reported as number and percentage. Continuous variables were compared using Student's *t*-test. Categorical variables were compared using Pearson's chi-square test or Fisher's exact test as appropriate. A *P*-value of less than 0.05 was considered statistically significant. Statistical analyses were conducted using the SPSS 15.0 statistical software program (SPSS Inc., Chicago, IL, USA).

3 Results

3.1 Demographics and pre-operative clinical information

Nighty-one patients (58 females and 33 males) successfully underwent LDP (*n*=45) or ODP (*n*=46) for a benign or premalignant tumor of the distal pancreas during the study period. Between the LDP and ODP groups, there were no significant intergroup differences in the following clinical factors: age, sex, or body mass index (BMI) (Table 1). The final histological results were as follows: neuroendocrine tumor (21), serous cystic neoplasm (32), solid pseudopapillary tumors (17), mucinous cystic neoplasm (13), and intraductal papillary mucinous neoplasm (8) (Table 2).

Table 1 Demographic and pathologic characteristics of patients undergoing ODP and LDP

| Group | Age (year) | Number | | BMI (kg/m^2)* | Number | | | HGB (g/L)* | Albumin (g/L)* |
		Male	Female		Diabetes mellitus	CVD	Chronic pancreatitis		
ODP	50.1±14.3	18	28	21.6±1.6	3	11	3	12.8±1.2	41.5±3.8
LDP	50.5±15.1	15	30	22.1±2.9	4	7	0	13.3±1.1	42.8±4.7
P-value	0.86	0.52		0.30	0.71	0.34	0.24	0.07	0.15

* Data are expressed as mean±SE (*n*=46 for ODP or *n*=45 for LDP). CVD: cardiovascular disorder; HGB: hemoglobin

Table 2 Final pathology diagnoses in ODP and LDP patients

Group	Number	Neuroendocrine tumor	Serous cystic neoplasm	Mucinous cystic neoplasm	Solid pesudopaplillary tumors	Intraductal papillary mucinous neoplasm
ODP	46	12	13	6	9	6
LDP	45	9	19	7	8	2
Total	91	21	32	13	17	8

Table 3 Intra-operative features of patients undergoing ODP and LDP

Group	Operative time (min)	Operative blood loss (ml)	Tumor size (cm)	Spleen preservation rate (%)	Conversion from ODP to LDP
ODP	92.2±24.1	203.1±84.8	4.5±1.8	47.8 (22/46)	
LDP	158.7±38.3	122.6±61.1	4.7±3.2	53.3 (24/45)	0
P-value	0	0	0.77	0.35	

Data are expressed as mean±SE (n=46 for ODP or n=45 for LDP) or percentage (count/total)

Table 4 Multivariable analyses of peri-operative outcome measures of patients undergoing ODP and LDP

Outcome	ODP	LDP	*P*-value
Total morbidity (%)	0	0	
Total operative complications (%)[a]	47.8 (22/46)	26.7 (12/45)	0.04
Extra-abdominal complications (n)			
Urinary tract infection	1	0	
Pulmonary infection	2	2	
Cardiovascular complication	2	0	
Abdominal complications (n)			
Bleeding	1	1	
Incision infection	3	0	
Intestinal adhesion	2	1	
Delayed gastric emptying	2	1	
Pancreatic fistula (%)[a]	19.6 (9/46)	15.6 (7/45)	0.62
Grade A (n)	7	5	1
Grade B (n)	2	2	1
Grade C (n)	0	0	
Time to resume normal daily activities (d)[b]	2.1±0.6	1.8±0.4	0.02
Post-operative time until oral intake (d)[b]	3.2±0.7	1.6±0.5	0
Post-operative length of hospital stay (d)[b]	11.9±5.8	7.9±3.8	0.006

[a] Data are expressed as percentage (count/total). [b] Data are expressed as mean±SE (n=46 for ODP or n=45 for LDP)

3.2 Intra-operative outcomes

No patient in the LDP group was converted to ODP. The median operative time in the LDP group was (158.7±38.3) min compared with (92.2±24.1) min in the ODP group (P<0.001). Intra-operative blood loss in the LDP group was lower than that in the ODP group ((122.6±61.1) ml vs. (203.1±84.8) ml, P<0.001). The rates of splenic conservation between the LDP and ODP groups were similar (53.3% vs. 47.8%, P=0.35). Splenic vessels were all preserved during spleen-preserving pancreatectomies. No obvious difference in tumor size between the groups was observed ((4.7±3.2) cm vs. (4.5±1.8) cm, P=0.77; Table 3).

3.3 Post-operative outcomes

No patient died in the ODP group or LDP group, or needed a re-operation. The overall post-operative complication rates were lower in the LDP group compared with the ODP group (26.7% vs. 47.8%, P=0.04; Table 4). The overall pancreatic fistula rates between the LDP and ODP groups were similar (15.6% vs. 19.6%, P=0.62). A pancreatic fistula developed in nine patients in the ODP group (7 Grade A and 2 Grade B) versus seven patients in the LDP group (5 Grade A and 2 Grade B). Time to oral intake and time to resume normal daily activities were significantly faster in the LDP group than in the ODP group ((1.6±0.5) d vs. (3.2±0.7) d, P<0.01; (1.8±0.4) d

vs. (2.1±0.6) d, *P*=0.02, respectively). The post-operative length of hospital stay was also shorter in the LDP group compared with the ODP group ((7.9±3.8) d vs. (11.9±5.8) d, *P*=0.006; Table 4).

4 Discussion

In this prospective two-center comparative study of clinical outcomes for LDP and ODP, we demonstrated that LDP is a feasible, safe, and efficient approach for benign or premalignant pancreatic neoplasms. We observed less blood loss, an earlier return to normal bowel movement, and a significantly shorter post-operative length of stay in the LDP group compared with ODP. The overall morbidity in our study was not different between the LDP and ODP groups, indicating similar safety profiles of the two surgical approaches. These findings are consistent with the best case series published so far (Baker *et al.*, 2009; Casadei *et al.*, 2010; Vijan *et al.*, 2010; Abu Hilal *et al.*, 2012; Soh *et al.*, 2012).

The highlight of this study is that all the pancreatic lesions in the two groups were benign or of low grade. The pathology and the lesion's size are two main factors that influence the operative difficulty during a distal pancreatectomy. When we compare LDP with ODP, the operative difficulty between two groups should be taken into account because it will influence the feasibility and peri-operative outcomes, such as blood loss, operation time, splenic conservation rate, and morbidity. Further, it is notable that the LDP and the ODP in our study were practiced by specialized surgeon teams in two high-volume centers separately, who specifically focus on laparoscopic pancreatic surgery and the open pancreatic approach. Thus, the selection bias in this two-center comparative study can be avoided to a certain degree.

In contrast to most studies showing that LDP had shorter operation time, we observed a converse result: the median operative time in the LDP group was longer than that in the ODP group. We can rationalize this difference by the skilled practice of the open surgery team. In fact, the operation times of the LDP ((158.7±38.3) min) and ODP ((92.2±24.1) min) groups in our study are shorter than most of the former studies, which reflects benign pathology of all the lesions.

Another interesting finding of our study is the high rate of splenic conservation in the LDP group (55.6%). The patients who underwent laparoscopic spleen-preserving distal pancreatectomy had significantly shorter operative time and less blood loss compared with those who underwent concomitant splenectomy (Shoup *et al.*, 2002; Goh *et al.*, 2008; Lee *et al.*, 2008; Mekeel *et al.*, 2011; Butturini *et al.*, 2012). The rate of splenic conservation in former studies of LDP varied from 2% to 70% (Shoup *et al.*, 2002; Goh *et al.*, 2008; Lee *et al.*, 2008; Casadei *et al.*, 2010; Vijan *et al.*, 2010; Abu Hilal *et al.*, 2012; Butturini *et al.*, 2012). However, most of the former comparative studies included both malignant and benign lesions. Therefore, the high rate of spleen preservation may be attributed to the high rate of malignant lesions in the open group, and the fact that many lesions in the open group were inflammatory strictures secondary to pancreatitis. In our study, considering that all the lesions were benign in both the LDP and the ODP groups, the higher rate of splenic conservation in the LDP group demonstrates a noteworthy advantage of LDP over ODP.

Spleen conservation could be achieved by carefully dissecting the splenic vessels off the pancreas parenchyma or by resecting the main splenic vessels en bloc with the pancreas but maintaining the short gastric vessels and left gastroepiploic arcade to ensure the collateral blood supply to the spleen (Warshaw, 1988). In our study, spleen conservation was accomplished by preserving the main splenic artery and vein. We think that the better vision afforded by the magnification using the laparoscopic instrument and the subtle laparoscopic manipulations available assist in the fine dissection of the pancreas off the splenic artery and vein, resulting in higher splenic conservation rates.

The incidence of post-operative pancreatic fistula, the most common major morbidity after distal pancreatectomy, was not different in this study. Encompassing all grades of fistula, we observed a fistula rate of 15.6% in the LDP group, which is comparable or favorable to that reported by others. Several studies investigated different approaches to prevent pancreatic fistula in distal pancreatectomy. However, none of these methods could reduce the rate of pancreatic fistula significantly. In this study, we routinely used the mechanical linear staplers. The LDP group used

small staples (2.5–3.5 mm) depending on the texture of the pancreas (2.5 mm for thin pancreases and 3.5 mm for thick pancreases), whereas the ODP prefers large staples (4.5 mm).

In this study, the pre-operative variables such as demographics, blood profiles, and co-morbid conditions were comparable between the two groups, indicating that patients are relatively alike in terms of their pre-operative status and subsequent comparisons are more meaningful. Although we attempted to circumvent selection bias, a certain degree of bias is inherent between the two institutions in the comparative study. Another limitation of this study is the relatively small number of cases. As distal pancreatectomy is an infrequent procedure, enrolment of large numbers of cases may be a difficult task.

In summary, the findings in this study confirmed the safety and efficacy of LDP for the treatment of benign and premalignant lesions in the pancreatic body and tail. This laparoscopic approach is associated with less operative blood loss and hospitalization fast recovery compared with ODP. LDP may be progressively adopted as the "gold standard" for the management of benign and premalignant pancreatic lesions. Further studies on the oncologic quality and more prospective randomized comparative trials for LDP should be performed before applying this to the management of pancreatic malignancies.

Compliance with ethics guidelines

Jia-fei YAN, Tian-tao KUANG, Da-yong JI, Xiao-wu XU, Dan-song WANG, Ren-chao ZHANG, Wei-wei JIN, Yi-ping MOU, and Wen-hui LOU declare that they have no conflict of interest.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from all patients for being included in the study.

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中文概要

题　目：腹腔镜与开腹胰体尾切除术双中心对照研究

目　的：评估腹腔镜胰体尾切除术安全有效性，对比腹腔镜胰体尾切除术与开腹胰体尾切除术治疗胰腺体尾部良性或低度恶性病变临床疗效。

创新点：本研究为回顾性对照研究，相较于过往腹腔镜胰体尾切除术与开腹胰体尾切除术的对照研究，其创新点一为本组 91 例病例均为良性或低度恶性病例，剔除了恶性病变病例；二为本研究中腹腔镜胰体尾切除术组及开腹胰体尾切除术组分别由两家大型综合医院胰腺疾病诊治中心的两组医生分别施行手术，这样避免了病人及手术方式选择等造成的影响，结果更为客观。

方　法：回顾分析自 2010 年 1 月至 2012 年 12 月浙江大学医学院附属邵逸夫医院 45 例施行腹腔镜胰体尾切除术治疗胰腺体尾部良性或低度恶性病变病例（LDP 组），以及同期上海复旦大学附属中山医院 46 例施行开腹胰体尾切除术胰腺体尾部良性或低度恶性病变病例（ODP 组）的相关临床资料，进行对照研究。

结　论：本研究包括胰腺体尾部良性或低度恶性病例 91 例，其中 LDP 组 45 例（无中转开腹）和 ODP 组 46 例。手术时间分别为(158.7±38.3) min（LDP 组）和(92.2±24.1) min（ODP 组）；术中出血 LDP 组明显少于 ODP 组（(122.6±61.1) ml vs. (203.1±84.8) ml，$P<0.001$）。两组保脾率相似（53.3% vs. 47.8%，$P=0.35$），其中 LDP 组中保脾病例均保留脾血管。在术后恢复指标方面，LDP 组优于 ODP 组，恢复进食流质时间((1.6±0.5) d vs. (3.2±0.7) d，$P<0.01$)及恢复活动时间((1.8±0.4) d vs. (2.1±0.6) d，$P=0.02$)较短，且 LDP 组术后住院时间也少于 ODP 组((7.9±3.8) d vs. (11.9±5.8) d，$P=0.006$)。术后胰瘘率两组无明显差异（15.6% vs. 19.6%，$P=0.62$），但术中总并发症率 LDP 组低于 ODP 组（26.7% vs. 47.8%，$P=0.04$）。研究结果显示腹腔镜胰体尾切除术治疗胰腺体尾部良性或低度恶性肿瘤安全可行，与开腹胰体尾切除术相比术中出血更少、术后恢复更快，具有明显微创优势。

关键词：胰腺肿瘤；腹腔镜；胰体尾切除术