Laparoscopic versus open pancreatic resection for ductal adenocarcinoma: separate propensity score matching analyses of distal pancreatectomy and pancreaticoduodenectomy

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Abstract

**Background:** Pancreatic ductal adenocarcinoma (PDAC) is one of the most leading causes of cancer mortality worldwide. Laparoscopic pancreatic resection (LPR) has been widely used in the treatment of benign and low-grade pancreatic diseases. It is necessary to expand the current knowledge on the feasibility and safety of LPR for PDAC. Laparoscopic distal pancreatectomy (LDP) and pancreaticoduodenectomy (LPD) are two main surgical approaches for PDAC. We performed separate propensity score matching (PSM) analyses, aiming to assess the surgical and oncological outcomes of LPR for PDAC by comparing LDP with open distal pancreatectomy (ODP) as well as LPD with open pancreaticoduodenectomy (OPD).

**Methods:** Data of patients who underwent DP and PD for PDAC from January 2004 to February 2020 in our hospital were obtained. Baseline characteristics, intraoperative effect, postoperative recovery, and survival outcomes were compared. One-to-one PSM was used to minimize selection biases by balancing factors including age, sex, BMI, and tumor size.

**Results:** Patient demographics were well matched after PSM. The DP subgroup included 86 LDP patients and 86 ODP patients, whereas the PD subgroup included 101 LPD patients and 101 OPD patients. Compared to ODP, LDP was associated with shorter operative time, less blood loss, and comparable overall morbidity. Of the 101 patients who underwent LPD, 10 patients (9.9%) required conversion to laparotomy. LPD was associated with longer operative time, less blood loss, and comparable overall morbidity. For oncological and survival outcomes, there were no significant differences in tumor sizes, R0 resection rate and tumor stage in both DP and PD subgroup. However, laparoscopic procedures seem to have an advantage over open surgery in terms of retrieved lymph node (DP subgroup: 14.4 ± 5.2 vs. 11.7 ± 5.1, \(p = 0.03\); PD subgroup 21.9 ± 6.6 vs. 18.9 ± 5.4, \(p = 0.07\)). There was no statistical significance between both groups in recurrence pattern, and 3-year recurrence-free and overall survival were comparable between groups.

**Conclusions:** Both LDP and LPD are feasible and oncologically safe procedures for PDAC. Postoperative outcomes and long-term survival of LDP and LPD are not inferior or superior to open surgery. However, the short-term surgical advantage of LPD is not as obvious as LDP mainly due to the conversions. Our findings should be further evaluated by multicenter or randomized controlled trials.

Introduction

Pancreatic duct adenocarcinoma (PDAC) is currently the fourth leading cause of cancer-related deaths in developed countries and may rank second by the year 2030 [1, 2]. Surgical resection is considered the only method to radically cure this type of cancer [3]. The surgical extent depends on the tumor location: left-sided PDAC should be treated by subtotal or distal pancreatectomy (DP), and PDAC on the pancreatic head are amendable to pancreaticoduodenectomy (PD). Minimally invasive surgery (MIS), characterized by laparoscopic interventions, have become the standard of care for many surgical procedures across
different specialties. The selection of MIS is the professional objective of surgeons and the most acceptable treatment for patients [4]. Regarding pancreatectomy, while the feasibility and safety of laparoscopic DP (LDP) have been gradually assessed [5], laparoscopic PD (LPD) for PDAC is still in its infancy due to the complexity of the operation and the steep learning curve required for its introduction [6, 7]. The Miami International Evidence-based Guidelines suggested that LPD should be exclusive to experienced surgeons in high-volume centers [8]. On the other hand, very few data of laparoscopic pancreatic resection (LPR) to date focus on PDAC and oncological outcomes are available. Challenges included the anticipated difficulties in accrual and standardization, lack of equipoise, and the preference of surgeons [9]. In other words, the therapeutic role of LP in the setting of PDAC is not yet established [10, 11]. Considering the different nature between LDP and LPD, it is reasonable to separately analyze LDP and LPD for the treatment of PDAC. We primitively proposed LDP as early as 2003 [12], and conducted LPD for the treatment of PDAC in 2012 after getting extensive laparoscopic experience [13, 14]. In this study, we evaluated the feasibility and safety of LDP and LPD by separately comparing its short- and long-term clinical outcomes with those of open DP (ODP) and PD (OPD).

**Materials And Methods**

**Study design and definitions**

This study was approved by the Ethics Committee of Zhejiang University. Written consent was obtained from every patient prior to surgery. Patients diagnosed with PDAC from January 2004 to February 2020 were identified from prospectively maintained pancreatic database. The diagnosis of PDAC was based primarily on preoperative imaging, specifically abdominal computed tomography or magnetic resonance imaging. Surgical procedures for PDAC included DP and PD. We routinely conducted multi-disciplinary team treatment models for every major abdominal surgery during which the decision to perform either laparoscopic or open approaches would be discussed followed by a presentation to patients and their families to make a final decision. Patients with any of the following conditions were excluded: 1) palliative resection; 2) distant metastasis; 3) few cases of total pancreatectomy (TP) for PDAC were excluded from this study. Prior abdominal surgery was not considered a contraindication to offering laparoscopic surgery.

The DP group patients were divided into two groups: those undergoing LDP and those undergoing ODP. To minimize selection biases, 1:1 propensity score matching (PSM) was performed using a logistic regression model and the following covariates: age, sex, body mass index (BMI), and tumor size. Patients for whom the propensity score could not be matched exactly were excluded. The PD group patients were dealt with in the same way. A flow chart of patient selection is shown in Fig. 1. Patients were evaluated in an intention-to-treat (ITT) fashion. Data on patient demographics, clinical presentation, surgical outcomes, tumor characteristics, lymph node status, resection margins, and long-term oncologic outcomes were compared. For the LPD group, we also compared the effect of conversion to laparotomy with that of complete resection under laparoscopy since there was relatively high conversion rate in LPD for the treatment of PDAC to assess the impact of conversion. Postoperative pancreatic fistulas (POPF)
were defined and classified according to the 2016 updated International Study Group on Pancreatic Surgery definitions, in which Grade B and C were considered “clinically relevant POPF (CR-POPF)” [15]. Complications were recorded using the Clavien–Dindo classification system [16], in which Graded I and II were grouped as minor, and graded III-V was considered as major complications. Oncologic outcomes were analyzed for all patients, including tumor size (maximum dimensions; cm), total number of lymph nodes (LNs), and margin status. Resection margins were considered negative (R0) when no tumor was evident along the transection surface [17]. Tumor recurrence was graded as locoregional, extrapancreatic, and multiple. Locoregional recurrences included tumors in adjacent organs, pancreatic remnants, or locoregional LNs. Extrapancreatic recurrences included peritoneal, distant lymphatic or hematogenous metastases. Radiologic evidence of intra-abdominal soft tissue around the operative site and/or distant metastases was defined as tumor recurrence. Disease-free survival (DFS) was defined as the time between surgery and diagnosis of recurrence or censoring. Overall survival (OS) was defined as the time between the date of surgery and the date of death from any cause or censoring.

Operative Procedure

Details of the various operative procedures were previously described [18–20]. Five ports were inserted for the surgeon and the assistant. The surgical extension and protocol was the same as in open surgeries. Standard lymphadenectomy was used in LDP, which includes at least LN located in the hilum of the spleen (No. 10), along the splenic artery (No. 11), and along the inferior border of the body and tail of the pancreas (No. 18). LN located around the celiac axis was also included in the tumors of the pancreatic body [21]. Dissection was performed mainly in a right-to-left manner. The splenic artery and vein were divided at the root. The soft tissue around the common hepatic artery and celiac trunk were dissected. Then, dissection was performed in a “medial-to-lateral” fashion, and the distal pancreas along with the spleen was removed. The lymphadenectomy for LPD included the following LN stations: 5 (suprapyloric), 6 (infrapyloric), 8a (common hepatic artery), 12b-c (along the bile duct and cystic duct), 13a-b (along the head of the pancreas), 14a-b (along the right lateral side of superior mesenteric artery), and 17a-b (along the anterior face of the head of the pancreas). Retroperitoneal soft-tissue was completely removed. The intracorporeal Child’s approach was used for the reconstruction along the same principles of in pancreaticojejunostomy (PJ). An end-to-side PJ was conducted as long as a maximum diameter of 2 mm was attained at the pancreatic duct, in spite of the difficulty in identification, while the duct-to-mucosa PJ could be utilized in cases where the pancreatic ducts were over a diameter of 2 mm. All specimens and their margins were routinely sent for intra-operative frozen section examinations.

Statistical analysis

We used SPSS version 23.0 (IBM Corp., Armonk, NY) to perform all statistical analysis. Analysis was performed in the intention to treat population, that is, all patients who received the allocated intervention. Continuous variables are expressed as mean and standard deviation (SD) when the distribution was considered normal, and otherwise using the median, and range. Categorical variables are expressed as
absolute numbers and percentages. The Student $t$ test or the Mann–Whitney $U$ test was used for the comparison of continuous variables and the chi-square Chi-square test or the Fisher exact test for categorical variables, depending on the conditions of application. Survival rates and comparisons were estimated by the Kaplan–Meier survival curves and the log-rank test. All reported $p$ values are 2-sided. Values of $p < 0.05$ were considered to indicate statistically significant differences.

Results

Patient selection and clinicopathological characteristics

During the study period, 699 patients meeting the inclusion and exclusion criteria were selected, of which 283 patients undergoing DP (135 LDP and 148 ODP) and 416 patients undergoing PD (128 LPD and 288 OPD). After separate PSM, 86 patients were matched in DP subgroup and 101 patients were matched in PD subgroup (Fig. 1). Details of baseline characteristics of LDP versus ODP and LPD versus OPD were described in Table 1. Patient characteristics of age, sex, BMI, and ASA were well matched by PSM. There were no differences between the LDP and ODP groups regarding the comorbidity, previous abdominal surgery, and the preoperative blood tests of CA19-9 and bilirubin. As to PD, 6 (5.9%) and 9 (8.9%) patients in the LPD and OPD groups respectively had undergone abdominal laparotomy previously for other reasons ($p = 0.42$). Preoperative median bilirubin level was similar between the LPD and OPD groups ($p = 0.44$). Preoperative median CA19-9 level was also similar, with 125.7 IU/mL in the LPD group and 145.7 IU/mL in the OPD group ($p = 0.95$).
Table 1
Separate comparison of demographics and clinical characteristics.

| Variable                                      | LDP (n = 86)       | ODP (n = 86)       | p value | LPD (n = 101)      | OPD (n = 101)      | p value |
|-----------------------------------------------|--------------------|--------------------|---------|--------------------|--------------------|---------|
| Age (years)<sup>a</sup>                      | 62.7 ± 8.7         | 62.9 ± 8.8         | 0.90    | 62.4 ± 8.2         | 62.2 ± 8.4         | 0.87    |
| Gender (Male: Female)                        | 54: 32             | 54: 32             | 1.00    | 67: 34             | 67: 34             | 1.00    |
| BMI (kg/m<sup>2</sup>)<sup>a</sup>           | 22.5 ± 2.5         | 22.3 ± 2.3         | 0.53    | 22.3 ± 2.5         | 22.5 ± 2.6         | 0.58    |
| ASA classification (I:II:III)                | 40: 43: 3          | 41: 42: 3          | 0.99    | 47: 52: 2          | 45: 54: 2          | 0.96    |
| Presence of comorbidity (Yes:No)             | 38: 48             | 36: 50             | 0.76    | 44: 57             | 46: 55             | 0.78    |
| Hypertension                                 | 26                 | 20                 |         | 22                 | 31                 |         |
| Diabetes mellitus                            | 17                 | 15                 |         | 15                 | 16                 |         |
| Cardiovascular                               | 2                  | 1                  |         | 3                  | 3                  |         |
| Pulmonary                                    | 5                  | 4                  |         | 5                  | 2                  |         |
| Hepatic                                      | 2                  | 1                  |         | 3                  | 0                  |         |
| Others                                       | 1                  | 1                  |         | 3                  | 2                  |         |
| Previous abdominal surgery (%)               | 7 (8.1%)           | 8 (9.3%)           | 0.79    | 6 (5.9%)           | 9 (8.9%)           | 0.42    |
| Preoperative CA19-9 (IU/mL)<sup>b</sup>     | 108.9 (1.6–3111.0) | 113.2 (4.1–3542.0) | 0.40    | 125.7 (4.4–5041.0) | 145.7 (1.5–5113.0) | 0.95    |
| Preoperative bilirubin (µmol/L)<sup>b</sup>  | 11.8 (4.6–28.3)    | 12.5 (5.2–24.3)    | 0.74    | 83.5 (4.7–320.8)   | 94.0 (5.9–390.8)   | 0.44    |

<sup>a</sup> values were showed as mean (standard deviation) and tested by Student’s t test; <sup>b</sup> values were showed median (range) and tested by Mann-Whitney U test. BMI body mass index, ASA American Society of Anesthesiologists.
Surgical Data And Postoperative Outcomes

Surgical data and postoperative outcomes were summarized in Table 2. In LDP, one conversion was needed because of adhesions that impeded access to lymphadenectomy. Another two conversion were due to bleeding from splenic vessels. In the LDP group, the mean operative time was significantly short (189.1 ± 45.2 vs. 213.3 ± 54.4 min, $p<0.01$), and median blood loss was significantly less than in the ODP group (180 [80–600] vs. 220 [120–800] mL, $p<0.01$). Also, a less red blood cell transfusion were observed in the LDP group (3.5% vs. 11.6%, $p = 0.04$). In addition, the median postoperative hospital stay for the LDP patients was significantly shorter than for the ODP patients (9 [4–34] vs. 13 [7–42] days, $p<0.01$).
Table 2
Separate comparison of surgical data and postoperative outcomes.

| Variable                               | LDP (n = 86) | ODP (n = 86) | p value | LPD (n = 101) | OPD (n = 101) | p value |
|----------------------------------------|--------------|--------------|---------|---------------|---------------|---------|
| Operative time (min)\(^a\)             | 189.1 ± 45.2 | 213.3 ± 54.4 | < 0.01  | 416.2 ± 78.8  | 365.0 ± 81.6  | < 0.01  |
| Estimated blood loss (mL)\(^b\)        | 180 (80–600) | 220 (120–800) | < 0.01  | 250 (150–900) | 300 (180–1000) | 0.04    |
| RBC transfusion (%)                    | 3 (3.5%)     | 10 (11.6%)   | 0.04    | 14 (13.9%)    | 22 (21.8%)    | 0.14    |
| Postoperative hospital stay (days)\(^b\)| 9 (4–34)     | 13 (7–42)    | < 0.01  | 14 (9–69)     | 18 (11–52)    | < 0.01  |
| Overall morbidity (n, %)               | 8 (9.3%)     | 14 (16.3%)   | 0.17    | 22 (21.8%)    | 32 (31.7%)    | 0.11    |
| CR-POPF                                | 5            | 7            |         | 12            | 16            |         |
| Delayed gastric emptying               | 0            | 3            |         | 6             | 10            |         |
| Hemorrhage                             | 0            | 2            |         | 5             | 6             |         |
| Bile leak                              | 0            | 0            |         | 2             | 3             |         |
| Wound infection                        | 0            | 2            |         | 1             | 1             |         |
| Lymphorrhoea                           | 1            | 0            |         | 0             | 2             |         |
| Pulmonary complications                | 2            | 2            |         | 2             | 5             |         |
| Reoperation (%)                        | 0            | 0            | 1.00    | 6 (5.9%)      | 8 (7.9%)      | 0.58    |
| Clavien-Dindo classification           |              |              | 0.33    |               |               | 0.42    |

\(^a\) values were showed as mean (standard deviation) and tested by Student’s t test; \(^b\) values were showed median (range) and tested by Mann-Whitney U test.
| Variable                  | LDP (n = 86) | ODP (n = 86) | p value | LPD (n = 101) | OPD (n = 101) | p value |
|---------------------------|--------------|--------------|---------|---------------|---------------|---------|
| I-II                      | 4            | 5            |         | 10            | 16            |         |
| III-IV                    | 4            | 9            |         | 11            | 15            |         |
| V (90-day mortality)      | 0            | 0            |         | 1             | 1             |         |
| Adjuvant treatment (%)    | 61 (70.9%)   | 57 (66.3%)   | 0.51    | 67 (66.3%)    | 65 (64.4%)    | 0.77    |
| Time to adjuvant treatmenta | 50 (28–82)  | 52 (26–88)   | 0.14    | 59 (26–98)    | 60 (26–103)   | 0.68    |

a: values were showed as mean (standard deviation) and tested by Student’s t test; b: values were showed median (range) and tested by Mann-Whitney U test.

For the 101 LPD cases, conversion to open surgery was necessary in 10 (9.9%) because of a severe adhesion caused by historical abdominal surgery (n = 1), intraoperative uncontrollable bleeding from the branches of major vessels (superior mesenteric artery, n = 2; gastroduodenal artery, n = 2; portal vein, n = 3), and suspicious vascular invasion to achieve safe margins (n = 2). LPD showed longer operative time than OPD (416.2 ± 78.8 vs. 365.0 ± 81.6 min, p < 0.01). LPD showed less blood loss (250 [150–900] vs. 300 [180–1000] mL, p = 0.04), but the difference of blood transfusion did not reach statistical significance (13.9% vs. 21.8%, p = 0.14). The median hospital stay was longer in the OPD group than in the LPD group (14 [9–69] vs. 18 [11–52] days, p < 0.01). Two in-hospital mortalities were noted: each group had one severe postoperative pancreatic fistula (POPF), and the patients died of multisystem organ failure secondary to sepsis. 22 (21.8%) patients in the LPD group and 32 (31.7%) in the OPD group experienced postoperative complications (21.8% vs. 31.7%, p = 0.11). For specific complications, CR-POPF (12 vs. 16), delayed gastric emptying (DGE) (6 vs. 10) and pulmonary complications (2 vs. 5) were more frequent in the OPD group; however, all these differences between the groups did not attain statistical significance. The severity of morbidity according to the Clavien–Dindo classification was comparable between LPD and OPD groups (p = 0.42).

**Comparison Of Completely Lpd With Conversion To Open Procedure**

As shown in Table 3, no significant differences between the complete laparoscopy and conversion groups with regard to age, sex, ASA score, comorbidity, previous abdominal surgery, preoperative CA19-9, bilirubin except for the BMI, which was higher in conversion group than that in complete group (21.9 [17.4–27.7] vs. 24.2 [20.8–28.3], p = 0.02). For surgical outcomes, operative time was comparable between the complete laparoscopy and conversion groups, but blood loss was significantly less in complete group
(240 [150–800] vs. 550 [200–900] mL, $p < 0.01$). The median postoperative hospital stay was longer in the conversion group (14 [9–69] vs. 17.5 [14–38] days, $p < 0.01$). In addition, a complete laparoscopy was associated with lower morbidity compared to a conversion to open procedure (18.7% vs. 50%, $p = 0.04$).
Table 3  
Comparison of completely LPD with these conversion to open procedure.

| Variable                              | Conversion (n = 10) | Complete (n = 91) | p value |
|---------------------------------------|--------------------|-------------------|---------|
| Age (years)                           | 64.5 (52–75)       | 63 (45–80)        | 0.55    |
| Gender (Male: Female)                 | 5: 5               | 62: 29            | 0.30    |
| BMI (kg/m²)                           | 24.2 (20.8–28.3)   | 21.9 (17.4–27.7)  | 0.02    |
| ASA classification (I:II:III)         | 5: 5: 0            | 42: 47: 2         | 0.88    |
| Presence of comorbidity (Yes:No)      | 4: 6               | 40: 51            | 0.81    |
| Previous abdominal surgery            | 1 (10%)            | 5 (5.5%)          | 0.47    |
| Preoperative CA19-9 (IU/mL)           | 177.5 (40.4–1790.0)| 120.4 (4.4–5041.0)| 0.47    |
| Preoperative bilirubin (µmol/L)       | 64.0 (8.3–320.8)   | 87.4 (4.7–303.1)  | 0.57    |
| Operative time (min)                  | 455 (320–490)      | 400 (270–680)     | 0.39    |
| Estimated blood loss (mL)             | 550 (200–900)      | 240 (150–800)     | <0.01   |
| Postoperative hospital stay (days)    | 17.5 (14–38)       | 14 (9–69)         | <0.01   |
| Overall morbidity (n, %)              | 5 (50%)            | 17 (18.7%)        | 0.04    |
| Reoperation (%)                       | 1 (10%)            | 5 (5.5%)          | 0.47    |
| Tumor size                            | 3.5 (1.5–5.0)      | 3.0 (1.5–5.4)     | 0.56    |
| Radical R0 resection (%)              | 8 (80%)            | 86 (94.5%)        | 0.14    |
| Retrieved lymph node                  | 20 (16–30)         | 22 (13–54)        | 0.47    |
| Vascular invasion (%)                 | 3 (30%)            | 14 (15.4%)        | 0.37    |
| Perineural invasion (%)               | 6 (60%)            | 38 (41.8%)        | 0.33    |

Note: all continuous data were showed as median (range) and compared by Mann-Whitney U test due to abnormal distribution in conversion group.

Pathology Examination And Oncological Outcomes
Pathology examination outcomes are listed in Table 4. There was no difference in tumor size, cell differentiation, pT stage, and pN stage between the LDP and ODP groups. The LDP group was associated with a significantly higher number of harvested LNs than the ODP group (14.4 ± 5.2 vs. 12.7 ± 5.0, \( p = 0.03 \)), whereas the radical R0 resection rates, vascular, and perineural invasion were comparable between the LDP and ODP groups. After PSM, pathological examination revealed that tumor size, pT-stage, and pN-stage were well matched between the LPD and OPD groups. The LPD group tended to have more harvested LNs than the OPD group (22.6 ± 6.5 vs. 21.0 ± 6.2, \( p = 0.07 \)). The R0 rates, vascular, and perineural invasion were similar between the LPD and OPD groups.
Table 4
Separate comparison of pathology examination.

| Variable                              | LDP (n = 86) | ODP (n = 86) | p value | LPD (n = 101) | OPD (n = 101) | p value |
|---------------------------------------|--------------|--------------|---------|--------------|--------------|---------|
| Tumor sizea                           | 41. ± 1.5    | 4.2 ± 1.4    | 0.97    | 3.0 ± 0.9    | 3.1 ± 1.0    | 0.60    |
| Differentiation                       |              |              | 0.84    |              |              | 0.56    |
| Well                                  | 34           | 36           |         | 33           | 39           |         |
| Moderate                              | 31           | 27           |         | 40           | 40           |         |
| Poor                                  | 21           | 23           |         | 28           | 22           |         |
| Radical R0 resection (%)              | 83 (96.5%)   | 78 (90.7%)   | 0.12    | 94 (93.1%)   | 90 (89.1%)   | 0.32    |
| Retrieved lymph nodea                 | 14.4 ± 5.2   | 12.7 ± 5.0   | 0.03    | 22.6 ± 6.5   | 21.0 ± 6.2   | 0.07    |
| Vascular invasion (%)                 | 17 (19.8%)   | 18 (20.9%)   | 0.85    | 17 (16.8%)   | 20 (19.8%)   | 0.59    |
| Perineural invasion (%)               | 41 (47.7%)   | 38 (44.2%)   | 0.65    | 44 (43.6%)   | 45 (44.6%)   | 0.89    |
| Pathologic T stage                    |              |              | 0.93    |              |              | 0.97    |
| T1                                    | 3            | 4            |         | 14           | 15           |         |
| T2                                    | 44           | 45           |         | 72           | 72           |         |
| T3                                    | 39           | 37           |         | 15           | 14           |         |
| Pathologic N stage                    |              |              | 0.66    |              |              | 0.60    |
| N0                                    | 42           | 46           |         | 50           | 53           |         |
| N1                                    | 35           | 29           |         | 44           | 38           |         |
| N2                                    | 9            | 11           |         | 7            | 10           |         |

a: values were showed as mean (standard deviation) and tested by Student's t test.

The oncological outcomes were summarized in Table 5. The median follow-up times were 17 (2–120) months and 15.5 (3–108) months in the LDP group and ODP group, respectively. Recurrence occurred in
65 patients (75.6%) in the LDP group including 22 locoregional, 25 extrapancreatic, and 18 combined locoregional/extrapancreatic recurrences, and 70 patients (81.4%) in the ODP group including 18 locoregional, 26 extrapancreatic, and 26 multiple recurrences. There were no statistically significant differences as regard to DFS and OS between LDP and ODP groups (Fig. 2A, B).

Table 5
Separate comparison of oncological outcomes.

| Variable          | LDP (n = 86) | ODP (n = 86) | p value | LPD (n = 101) | OPD (n = 101) | p value |
|-------------------|--------------|--------------|---------|--------------|--------------|---------|
| Recurrence        | 65 (75.6%)   | 70 (81.4%)   | 0.35    | 73 (72.3%)   | 81 (80.2%)   | 0.19    |
| Initial sites of  |              |              | 0.47    |              |              | 0.35    |
| recurrence        |              |              |         |              |              |         |
| Locoregional      | 22 (33.8%)   | 18 (25.7%)   | 18 (24.7%) | 20 (24.7%)   |              |         |
| Extrapancreatic   | 25 (38.5%)   | 26 (30.2%)   | 36 (49.3%) | 33 (40.7%)   |              |         |
| Multiple          | 18 (20.9%)   | 26 (30.2%)   | 19 (26.0%) | 28 (34.6%)   |              |         |
| RFS               |              |              | 0.50    |              |              | 0.54    |
| 1-year            | 52.9%        | 48.0%        | 65.7%   | 58.4%        |              |         |
| 2-year            | 31.1%        | 29.2%        | 41.9%   | 36.3%        |              |         |
| 3-year            | 17.3%        | 17.5%        | 26.3%   | 24.5%        |              |         |
| OS                |              |              | 0.20    |              |              | 0.57    |
| 1-year            | 82.1%        | 73.3%        | 88.4%   | 77.2%        |              |         |
| 2-year            | 39.6%        | 30.0%        | 54.9%   | 49.2%        |              |         |
| 3-year            | 30.6%        | 24.6%        | 32.7%   | 32.4%        |              |         |
| Median survival   | 20 (17.1–22.9) | 17 (14.3–19.7) | 26 (18.8–33.2) | 23 (19.1–26.9) | |
| (95% CI)          |              |              |         |              |              |         |

RFS recurrence-free survival, OS overall survival, CI confidence interval.

The median follow-up times were 22 (2–63) months and 33 (3–124) months in the LPD and OPD groups, respectively. Recurrence occurred in 73 patients (72.3%) in the LPD group including 18 locoregional, 36 extrapancreatic, and 19 combined locoregional/extrapancreatic recurrences, and 81 patients (80.2%) in the OPD group including 20 locoregional, 33 extrapancreatic, and 28 multiple recurrences. There were also no statistically significant differences in recurrence patterns, DFS, and OS between LPD and OPD groups (Fig. 2C, D).
Discussion

Pancreatectomy with lymphadenectomy remains the first-line treatment option for early- and intermediate-stage PDAC. Although LDP have become important options for benign or low-grade tumors on pancreatic bodies and tails [5, 8], the use of LDP for PDAC remains controversial. Two recent international surveys documented that 19–31% of surgeons expected LDP to be inferior to ODP in PDAC treatment [22, 23] due to the challenges including the anticipated difficulties in accrual and standardization, lack of equipoise, and the preference of surgeons [9]. On the other hand, approaching PDs laparoscopically for diseases on pancreatic heads were less frequent owing to the intricacy of the dissection and the complexity of the pancreatoenteric and biliodigestive anastomoses [6, 10]. Moreover, LPD for PDAC is even in its infancy because of the extra concerns on the safety, and oncological efficacy [10]. Therefore, it is necessary to separately evaluate the efficacy of LDP and LPD for PDAC treatment. This study suggested that both LDP and LPD for PDAC were technically feasible and safe. LPD is a longer operation for PDAC compared to OPD, whereas LDP could finish faster than ODP. Consistently, both LDP and LPD exhibit the clear benefit of less blood loss and short hospitalization. LDP and LPD have no obvious advantages in decreasing the postoperative morbidity. LDP appears to hold potential advantages in terms of retrieved lymph node. In addition, long-term survival outcomes were comparable between laparoscopic and open surgery.

The feasibility of LPD was the major concern in adoption of this surgical technique, as a high conversion rate was reported, especially in the initial period. In this ITT analysis, the conversion rates were only 3.5% (3/86) for LDP cases, but 10 (9.9%) conversions were needed in LPD. Two recently published randomized clinical trials (RCTs) reported the conversion rates of LPD were more than 20% [24, 25]. A high conversion rate indicates that LPD for PDAC remains a challenging procedure. The most common reasons of conversions were uncontrollable hemorrhages or had suspected vessel involvement, which was similar to other publications of LPD for PDAC treatment [26, 27]. Nickel et al. reviewed six studies focusing on the learning curve of LPD and revealed the volume to reach a technical competency ranged from 10 to 60 cases depending on surgeons’ expertise [28]. It might partially explain the high conversion rate of the RCTs, although surgeons had at least 10 cases of LPD experience before anticipating the RCTs. In our center, the surgical team was competent for advanced laparoscopic procedure, including reconstruction of the gastrointestinal tract, intracorporeal suture and emergency hemostasis etc.. We believe training together in a relatively constant surgical team contribute to the surgical outcomes a lot, especially in emergencies during LPD which may turn into conversion. Interestingly, the conversion cases found to be associated with higher BMI. The advantage of less blood loss in LPD was more obvious when data on conversion were omitted (data not shown), and the difference of overall morbidity between LPD and OPD could reach statistical difference (17/91 [18.7%] vs. 32/101 [31.7%], \( p = 0.04 \)). We believe part of the reason of high conversion is that PDAC frequently induces substantial pancreatic inflammation in the pancreatic remnant, thus difficult to resect due to pronounced adhesions or infiltrations to the surrounding tissues or vessels. Portomesenterical vein (PV) involvement is a common clinical finding in PDACs, but is a situation that is frequently difficult to diagnose prior to surgery [29]. However, researchers strongly recommend that PV should be resected once detected involving with tumor which should be
performed by surgeons with considerable proficiency in vascular resection and reconstruction [30, 31]. Therefore, as to LPD, approaching appropriate cases that without vessel involvement or severe adhesions laparoscopically, avoiding obese or overweight patients in the learning curve would be helpful to reduce conversion [24].

Our data showed a shortened operative time in LDP, but a prolonged operative time in LPD compared to their counterparts. The former could be mainly due to the simple steps of LDP, and quick management of trocar incision could offset the operation time of laparoscopic resection. In contrast, LPD present a more arduous challenge for surgeons as not only the intricate dissection, but also the complicated gastrointestinal, pancreatic and biliary anastomoses, all of which are especially technically demanding and time-consuming. Our initial LPDs for PDAC lasted for nearly 600 minutes [19]. Currently, this can be completed in approximately 300–350 minutes [18]. Kendrick et al., in one of the largest single series currently available, described their initial LPD duration to be 460 min, which improved to 320 min after approximately 50 cases [32]. Stauffer et al., reported a median operative time of 518 min, which was significantly longer than that in open surgery (140 min) [27]. The learning curve can be overcome in high volume centers, with average LPD operative times decreasing to less than 400 min [33]. However, due to tumor biology and the aggressiveness of the disease process, LPD for PDAC treatments are not commonly performed making it difficult to overcome the associated learning curve [6]. A recent study from the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) demonstrated that longer operative times were independently associated with worse perioperative outcomes after pancreatic resections [34]. Therefore, we believe long duration is a definite disadvantage of TLPDs for PDAC treatments.

We found both LDP and LPD showed up a trend of less overall morbidity without statistical significance in contrast to ODP and OPD (DP: 9.3 vs. 16.3%, \( p = 0.17 \); PD: 21.8 vs. 31.7%, \( p = 0.11 \)). POPFs are widely regarded as the most ominous of complications following pancreatic resection and the best management for the pancreatic stump is still under debate various surgical procedures of pancreatic stump management after DP and anastomosis after PD have been devised to prevent POPFs in the conventional open surgery. There has yet to be a consensus on the best method of stump management and debates exist as to which procedure is optimum [35, 36]. With the advancements of laparoscopic surgical instruments and the accumulation of operative experience, reported methods in open surgery can be meticulously performed laparoscopically [6, 36]. DGE is not life threatening, but can have significant consequences such as patient discomfort, prolonged hospital stays, diminished nutritional status, and delays in initiation of adjuvant therapy [37, 38]. The pathogenesis of DGE is multifactorial. Given the improved access and visualization as well as the meticulous attention, laparoscopic approach could theoretically reduce DGE [39, 40]: 1) less influence on the organs and peritoneum leading to less seroperitoneum helping to alleviate of gastric dysrhythmias, 2) ameliorative pyloric or antral ischemia due to reservation of small vessels, and 3) mitigant pylorospasms secondary to denervation of the stomach and duodenum or jejunum. In addition, open procedures are reported to portend a higher risk of pleural effusions, pulmonary infections, and atelectasis than do minimally invasive ones [41, 42].
Oncologic safety and efficacy should be clearly demonstrated prior to a wide application of a new surgical approach. The long-term survival outcomes of MISs for common malignancies have conflicting results [43–45], leading to a constant controversy over MIS for cancer treatments. R0 resection is frequently referred to as a crucial factor, which is deemed the only hope for cure [46]. Tactile evaluation of tissue is not possible during laparoscopy and was presumed to lead to inadequate surgical margins. Nevertheless, our study revealed that the R0 resection of LDP and LPD are comparable to open surgery. In addition, our data showed the retrieved LNs of LPD were not inferior to those of OPD (22.6 ± 6.5 vs. 21.0 ± 6.2, p = 0.07), and LNs harvest of LDP was even superior to ODP (14.4 ± 5.2 vs. 12.7 ± 5.0, p = 0.03). Notably, the DIPLOMA study showed that LDP was associated with a higher R0 resection rate (67% vs. 58%) and lower number of LNs (14 vs.22) [47]. But, this pan-European PSM study found the lower LN retrieval with LDP hardly impact on median OS (28 months vs. 31 months) [47]. Generally speaking, studies including meta-analyses showed promising long-term outcomes of LDP for PDAC [48–51]. However, there were scarce evidences of survival up to date for LPD. A single-center study conducted by Asbun and Stauffer, reported a comparable long-term survival of 1-, 2-, 3-, 4-, and 5-years for OPD (68, 40, 24, 17, and 15%) and for LPD (67, 43, 43, 38, and 32%), respectively [27]. Kuesters et al., conducted a series of LPD, also reported a comparable 5-year survival rate between LPD (20%) and OPD (14%) for PDACs [52]. Croome et al., recorded that the progression-free survival was longer in LPD [26]. One hypothesis was that improved recovery after laparoscopic surgery helped to instigate multimodality therapies earlier, thus leading to survival benefits [26]. However, a retrospective analysis of the NCDB found that MIS did not improve use or initiation of adjuvant chemotherapy for patients with PDAC [53]. Moreover, the survival impact of the initiation time of adjuvant chemotherapy in patients with resected PDAC remains uncertain since studies showed conflicting results [54, 55]. In our opinion, as long as the principles of radical resection are observed, a technically similar oncologic resection could be performed regardless of whether the open or laparoscopic approach was used.

Limitations of this study include its retrospective design, sample size, absence of randomization, and short follow-up period. Although PSM was performed to balance the covariates, thus reducing selection bias, other factors cannot be ignored. In PD arm, the follow-up of LPD was shorter than that of OPD since LPD was initially conducted in late 2012. Also, ODP had been mainly performed in early years in contrast to LDP. This can give rise to bias, taking postoperative management for example. In recent era of enhanced recovery after surgery (ERAS), surgeons can be inevitably affected by the ERAS concept, including early mobilization, oral feeding, midthoracic epidural analgesia, and early removal of abdominal drain, which result in shorter length of hospital stay and functional recovery [56], in their postoperative management, leading to bias in favor of the LDP and LPD group. The short follow-up period of LDP and LPD is insufficient to provide adequate information on long-term outcomes. Additionally, the sample size limits the ability to draw precise conclusions, particularly with respect to several variables that appeared different between the groups but where significance was not reached.

**Conclusions**
The current separate analyses of LDP and LPD demonstrated that laparoscopic pancreatectomy for PDAC patients was safe and effective, which was associated with less blood loss and shorter hospital stay. However, the short-term surgical advantage of LPD is not as obvious as LDP mainly due to the conversions. Oncological outcomes of LDP and LPD were not inferior to traditional open procedures for the treatment of PDAC. Higher levels of evidence including controlled trials are needed to elucidate clear conclusions.

**Abbreviations**

PDAC: pancreatic ductal adenocarcinoma, LPR: laparoscopic pancreatic resection, LPD: laparoscopic pancreaticoduodenectomy, OPD: open pancreaticoduodenectomy, DP: distal pancreatectomy, MIS: minimally invasive surgery, PSM: propensity score matching, TP: total pancreatectomy, SD: standard deviation, LN: lymph node, ITT: intention-to-treat, ISGPF: International Study Group on Pancreatic Fistula, POPF: postoperative pancreatic fistula, CR-POPF: clinically relevant POPF, DFS: disease-free survival, OS: overall survival, PJ: pancreaticojejunostomy, RCT: randomized clinical trials, NSQIP: National Surgical Quality Improvement Program, PV: portomesenterical vein, DGE: delayed gastric emptying, ERAS: enhanced recovery after surgery, BMI: body mass index, ASA: American Society of Anesthesiologists, RBC: red blood cell.

**Declarations**

**Ethics approval and consent to participate**

This study was approved by the Ethics Committee of Zhejiang University. Written consent was obtained from every patient prior to surgery.

**Consent for publication**

Not applicable.

**Availability of data and materials**

The datasets generated and/or analyzed during the current study are not publicly available due to data privacy according to the license for the current study, but are available from the corresponding author on reasonable request.

**Competing interests**

The authors declare that they have no competing interests.

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**Authors' contributions**

CK, PY and HCJ wrote the manuscript; CK, MYP, CQL, ZRC, ZMZ, WGY, WXF, and YJF performed the operations; PY, HCJ and YJF reviewed the medical records and collected data; MYP and YJF proofread and revised the manuscript; all authors read and approved the final manuscript.

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Figures
Figure 1

Flow chart of patient selection and literature search strategy.
Figure 2

Kaplan-Meier survival curves. (A) Cumulative DFS between LDP and ODP. (B) Cumulative OS between LDP and ODP. (C) Cumulative DFS between LPD and OPD. (D) Cumulative OS between LPD and OPD.