

Total laparoscopic versus open pancreaticoduodenectomy for pancreatic ductal adenocarcinoma: a propensity score matching analysis with meta-analysis

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Abstract

Background

Pancreatic ductal adenocarcinoma (PDAC) is one of the leading causes of cancer mortality worldwide. Total laparoscopic pancreaticoduodenectomy (TLPD) have been used in the treatment of benign and low-grade diseases on the pancreatic head. It is necessary to expand the current knowledge on the feasibility and safety of TLPD for PDAC treatment. We aimed to assess the surgical and oncological outcomes of TLPD for patients with PDAC by comparing them with open pancreaticoduodenectomy (OPD).

Methods

Data regarding patients who underwent pancreaticoduodenectomy for PDAC treatment from January 2013 to January 2019 in our hospital were obtained. Baseline characteristics, intraoperative effects, postoperative recoveries, and survival outcomes were compared. To overcome selection bias, we performed a 1:1 match using propensity score matching (PSM) between TLPD and OPD. We also conducted a systematic review and meta-analysis.

Results

The original cohort included 276 patients (TLPD; 98 patients, OPD; 178 patients). After PSM, there were 89 patients in each group and the patient demographics were well matched. Of the 98 patients who underwent TLPD, 8 (8.2%) required conversions to laparotomies. Compared to OPD, TLPD could be performed with longer operative times, had less blood loss, and had lower overall morbidities. Regarding oncological and survival outcomes, there were no significant differences in tumor size, R0 resection rates and tumor stages between groups. However, TLPD had an advantage over OPD in terms of retrieved lymph nodes (21.9 ± 6.6 vs. 18.9 ± 5.4 , $p < 0.01$). There were no statistically significant differences between the groups in recurrence patterns, and the 3-year recurrence-free and overall survival rates were comparable between the two groups. Meta-analysis further confirmed that the TLPD were associated with longer operative times, less blood loss, shorter hospitalizations, lower morbidities, and a greater number of retrieved lymph nodes.

Conclusions

TLPD are feasible and oncologically safe procedures for PDAC treatments. Postoperative outcomes and long-term survival after TLPD are superior, or not inferior, to OPD, and could be a promising alternative to open surgery for PDAC treatments. Our findings should be further evaluated by multicenter or randomized controlled trials.

Background

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]. However, total laparoscopic PD (TLPD) for PDAC is still in its infancy due to the complexity of the operation and the steep learning curve required for its introduction [5, 6]. The Miami International Evidence-based Guidelines suggested that TLPD should be exclusive to experienced surgeons in high-volume centers [7]. TLPD concerns included the safety, since it is arguably the most complex pancreatic operation, and of oncologic efficacy when performed on patients with PDAC [8]. Therefore, the role of TLPD in the setting of PDAC is less established and quality data are limited [9]. In this study, we evaluated the feasibility and safety of TLPD by comparing their short- and long-term clinical outcomes with those of open PD (OPD) through a propensity score-matched analysis to minimize selection bias based on our more than 15 years of experience performing laparoscopic pancreatic surgeries [10]. In addition, a rapid systematic review with a meta-analysis was conducted to further determine whether TLPD are an acceptable alternative to open surgery for PDAC treatment.

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 2013 to January 2019 were identified from our prospectively maintained pancreatic database. The diagnosis of PDAC was based primarily on preoperative imaging, specifically abdominal computed tomography or magnetic resonance imaging. When we initially conducted PD laparoscopically, an epigastric auxiliary incision was sometimes made to facilitate the reconstruction and help us to accumulate experience, which was referred to as a laparoscopic assisted PD (LAPD). TLPDs are characterized by intracorporeal anastomoses without an auxiliary incisions. Cases of LAPD were excluded from this study since TLPD preserve the integrity of the abdominal wall which would create a minimally-invasive advantage for TLPD over LAPD. 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.

To minimize selection biases, a 1:1 propensity score matching (PSM) was performed using a logistic regression model and included the following covariates: age, sex, ASA grade, tumor size, and combined resection. Data on patient demographics, clinical presentation, surgical outcomes, tumor characteristics, lymph node status, resection margins, and long-term oncologic outcomes were compared. 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 (CR-POPF)” [11]. Complications were recorded using the Clavien–Dindo classification system [12]. Oncologic

outcomes were analyzed for all patients, including tumor size (maximum dimensions; cm), total number of lymph nodes (LNs), and margin status. The LN ratio was defined as the number of ([the number of affected LNs/total number of LNs] × 100%). Resection margins were considered negative (R0) when no tumor was evident along the transection surface [13]. 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. Recurrence-free survival (RFS) 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 [10, 14]. Five ports were inserted for the surgeon and the assistant. The surgical extension and protocol was the same as in open surgeries. The lymphadenectomy 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.

Meta-analysis

We searched PubMed, EMBASE, and the Cochrane Library for literature comparing TLPD vs. OPD outcomes in the treatment of PDAC up to December 2019 and broadened the search range by browsing the references of retrieved articles. The following search terms were used: "minimally invasive," "laparoscopy," "Whipple," "pancreaticoduodenectomy," "pancreatic ductal adenocarcinoma," and "pancreatic cancer." The language of the articles was limited to English. Review articles, overlap authors or centers, and articles without adequate statistical data were excluded. All searched articles were reviewed by three authors (K.C., Y.P., and C.J.H), and disagreement was resolved via discussion. The Newcastle–Ottawa Quality Assessment Scale (NOS) was utilized to evaluate the quality of the included studies.

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. For the meta-analysis, Review Manager ver. 5.1 (Nordic Cochrane Center, Copenhagen, Denmark) was used. The effect size was calculated using odds ratio (OR) for dichotomous variables and weighted mean difference (WMD) with 95% confidence interval (CI) for continuous data. To account for clinical heterogeneity, which refers to diversity in a sense that is relevant for clinical situations, we used the random effects model based on DerSimonian and Laird' s method. $p < 0.05$ was considered statistically significant.

Results

Patient selection and clinicopathological characteristics

During the study period, 276 patients (TLPD: 98 and OPD: 178) meeting the inclusion and exclusion criteria were selected. After PSM, 89 patients in the TLPD group and 89 patients in the OPD group were included in the final analysis. A flow chart of patient selection is shown in Fig. 1. Baseline characteristics of patients in both groups are shown in Table 1. There were no statistically significant baseline characteristic differences between the two groups. PSM enabled better comparability between the two groups.

Table 1
Demographics, clinical characteristics before and after matching of TLPD vs. OPD.

Variable	All patients			Propensity-matched patients		
	TLPD (n = 98)	OPD (n = 178)	p value	TLPD (n = 89)	OPD (n = 89)	p value
Age (years) ^a	63.2 ± 9.3	62.5 ± 9.5	0.54	62.7 ± 7.6	62.4 ± 8.2	0.80
Gender (Male: Female)	63:35	111:67	0.75	58:31	58:31	1.00
BMI (kg/m ²) ^a	22.1 ± 2.6	22.2 ± 3.1	0.88	22.1 ± 2.5	22.4 ± 3.0	0.44
ASA classification (I:II:III)	42:49:7	80:92:6	0.40	41:46:2	38:49:2	0.87
Presence of comorbidity (Yes:No)	44:54	81/97	0.92	40:49	42:47	0.76
Hypertension	22	60		19	29	
Diabetes mellitus	16	27		14	14	
Cardiovascular	7	5		3	3	
Pulmonary	5	6		5	2	
Hepatic	3	4		3	0	
Others	3	6		3	2	
Neoadjuvant chemotherapy (%)	4 (4.1%)	13 (7.3%)	0.29	3 (3.4%)	7 (7.9%)	0.19

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. BMI body mass index, ASA American Society of Anesthesiologists.

Surgical Data And Postoperative Outcomes

Surgical data and postoperative outcomes are summarized in Table 2. For the 98 TLPD cases, conversion to open surgery was necessary in 8 (8.2%) 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 = 1; portal vein, n = 1), suspicious vascular invasion to achieve safe margins (n = 2); and acidosis due to a long lasting pneumoperitoneum (n = 1). Before PSM, the OPD group had a higher proportion of combined resections (6.1% vs. 11.2%, p = 0.16), which were eliminated by PSM (5% vs. 5.6%, p = 1.00). TLPD showed longer operative times than OPD before PSM (425.5 ± 75.0 vs. 382.6 ± 85.4 min, p < 0.01), and the difference was even more obvious after PSM (426.1 ± 75.3 vs. 370.5 ± 85.3 min, p < 0.01). TLPD showed less blood loss (before PSM, 280 [120–900] vs. 400

[200–1500] mL, $p < 0.01$; after PSM, 260 [120–900] vs. 400 [200–1200) mL, $p < 0.01$], and fewer blood transfusions (before PSM, 16.3% vs. 30.3%, $p = 0.01$; after PSM, 15.7% vs. 28.1%, $p = 0.04$) before and after PSM. The median hospital stay (after PSM, 13 [8–69] vs. 19 [11–52] days, $p < 0.01$) was longer in the OPD group than in the LPD group. 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. After PSM, 31 patients in the OPD group and 17 in the TLPD group experienced postoperative complications (after PSM, 20.2% vs. 33.7%, $p = 0.02$). For specific complications, delayed gastric emptying (DGE) (5.6% vs. 11.2%, $p = 0.18$) and pulmonary complications (1.1% vs. 5.6%, $p = 0.11$) were more frequent in the OPD group; however, the difference between the groups did not attain statistical significance. Morbidity in the OPD group was serious according to the Clavien–Dindo classification, but the difference also did not attain statistical significance ($p = 0.12$).

Table 2

Surgical data and postoperative outcomes before and after matching of TLPD vs. OPD.

Variable	All patients		p value	Propensity-matched patients		
	TLPD (n = 98)	OPD (n = 178)		TLPD (n = 89)	OPD(n = 89)	p value
Operative time (min) ^a	425.5 ± 75.0	382.6 ± 85.4	< 0.01	426.1 ± 75.3	370.5 ± 85.3	< 0.01
Estimated blood loss (mL) ^b	280 (120–900)	400 (200–1500)	< 0.01	260 (120–900)	400 (200–1200)	< 0.01
RBC transfusion (%)	16 (16.3%)	54 (30.3)	0.01	14 (15.7%)	25 (28.1%)	0.04
Combined resection	6 (6.1%)	20 (11.2%)	0.16	5 (5.6%)	5 (5.6%)	1.00
Postoperative hospital stay (days) ^b	13.5 (8–69)	19 (9–72)	< 0.01	13 (8–69)	19 (11–52)	< 0.01
Overall morbidity (n, %)	20 (20.4%)	62 (34.8%)	0.01	17 (19.1%)	31 (33.7%)	0.02
CR-POPF	11 (11.2%)	29 (16.3%)	0.24	11 (12.4%)	15 (16.8%)	0.40
Delayed gastric emptying	5 (5.1%)	16 (9.0%)	0.24	5 (5.6%)	10 (11.2%)	0.18
Hemorrhage	4 (4.1%)	17 (9.6%)	0.10	4 (4.5%)	8 (9.0%)	0.23
Bile leak	2 (2.0%)	6 (3.4%)	0.41	2 (2.2%)	3 (3.4%)	0.50
Wound infection	0 (0%)	3 (1.7%)	0.27	0 (0%)	1 (1.1%)	0.50
Lymphorrhea	0 (0%)	2 (1.1%)	0.42	0 (0%)	2 (2.2%)	0.25
Pulmonary complications	2 (2.0%)	13 (7.3%)	0.07	1 (1.1%)	5 (5.6%)	0.11
Reoperation (%)	5 (5.1%)	13 (7.3%)	0.48	4 (4.5%)	6 (6.7%)	0.52
Clavien-Dindo classification			0.05			0.12
I-II	9	28		7	15	
III-IV	10	33		9	15	
V (90-day mortality)	1	1		1	1	

a: values were showed mean (standard deviation) and tested by Student's t test; b: values were showed median (range) and tested by Mann-Whitney U test. RBC: red blood cell.

Pathology Examination And Oncological Outcomes

Pathology examination outcomes are listed in Table 3. Before PSM, the TLPD group had smaller tumor sizes. After PSM, pathological examination revealed that tumor size, pT-stage, and pN-stage were well matched between the two groups. The TLPD group was associated with a significantly higher number of harvested LNs than the OPD group (21.9 ± 6.6 vs. 18.9 ± 5.4 , $p < 0.01$), whereas the radical R0 resection rates, positive LNs, and LN ratios were comparable between the two groups.

Table 3
Pathology examination before and after matching of TLPD vs. OPD.

Variable	All patients		p value	Propensity-matched patients		
	TLPD (n = 98)	OPD (n = 178)		TLPD (n = 89)	OPD (n = 89)	p value
Tumor size ^a	3.0 ± 0.9	3.5 ± 1.2	< 0.01	3.0 ± 0.9	3.0 ± 1.0	0.74
Differentiation			0.88			0.52
Well	31	62		29	35	
Moderate	41	72		35	35	
Poor	26	44		25	19	
R0 resection (%)	88 (89.8%)	148 (83.1%)	0.13	82 (92.1%)	78 (87.6%)	0.32
Retrieved lymph node ^a	21.8 ± 6.5	18.9 ± 5.7	< 0.01	21.9 ± 6.6	18.9 ± 5.4	< 0.01
Positive lymph node ^b	1 (0–14)	1 (0–11)	0.98	1 (0–14)	0 (0–10)	0.84
Lymph node ratio ^b	3.3 (0–50)	3.5 (0–50)	0.48	3.1 (0–50)	0 (0–50)	0.71
Pathologic T stage			0.24			0.89
T1	10	24		12	15	
T2	72	113		64	62	
T3	16	41		13	12	
Pathologic N stage			0.22			0.48
N0	45	87		42	45	
N1	45	66		40	34	
N2	8	25		7	11	

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.

The oncological outcomes are summarized in Table 4. The median follow-up times were 25 (10–58) months and 23 (10–83) months in the TLPD and OPD groups, respectively. Before PSM, recurrence occurred in 70 patients (71.4%) in the TLPD group including 19 (27.1%) locoregional, 33 (47.1%) extrapancreatic, and 18 (25.7%) combined locoregional/extrapancreatic recurrences, and 138 patients (77.5%) in the OPD group including 31 (17.4%) locoregional, 57 (32.0%) extrapancreatic, and 50 (28.1%)

multiple recurrences, without statistically significant difference between the two groups ($p = 0.26$). There were also no statistically significant differences in recurrence patterns ($p = 0.31$) between the two groups. However, statistically improved recurrence-free and overall survival outcomes (before PSM, median survival, 95% CI: 26 [20.4–31.6] vs. 19 [16.7–21.3] months, $p = 0.02$) were identified in the TLPD group as shown in Table 4, and Fig. 2A and Fig. 2B. After PSM, there was no difference in any of the values, indicating the procedures have equivalent oncologic outcomes. Although the TLPD group showed a slightly longer median survival time than the OPD group (25 [19.4–30.6] vs. 21 [17.4–24.6] months), there was no statistically significant difference in regard to survival outcomes between the two groups ($p = 0.29$) as shown in Table 4 and Fig. 2C Fig. 2D.

Table 4
Oncological outcomes before and after matching of TLPD vs. OPD.

Variable	All patients		Propensity-matched patients			
	TLPD (n = 98)	OPD (n = 178)	p value	TLPD (n = 89)	OPD (n = 89)	p value
Recurrence	70 (71.4%)	138 (77.5%)	0.26	62 (69.7%)	66 (74.2%)	0.51
Initial sites of recurrence			0.31			0.61
Locoregional	19 (27.1%)	31 (17.4%)		15 (24.2%)	16 (24.2%)	
Extrapancreatic	33 (47.1%)	57 (32.0%)		31 (50.0%)	27 (40.9%)	
Multiple	18 (25.7%)	50 (28.1%)		16 (25.8%)	23 (34.8%)	
RFS			0.04			0.29
1-year	62.5%	49.1%		62.1%	54.3%	
2-year	38.7%	28.2%		39.5%	31.5%	
3-year	20.6%	19.2%		21.8%	22.7%	
OS			0.02			0.29
1-year	88.5%	68.9%		87.4%	71.6%	
2-year	53.9%	37.8%		52.4%	44.0%	
3-year	31.8%	22.1%		33.3%	27.3%	
Median survival (95% CI)	26 (20.4–31.6)	19 (16.7–21.3)		25(19.4–30.6)	21(17.4–24.6)	
RFS recurrence-free survival, OS overall survival, CI confidence interval.						

Outcomes Of The Systematic Review And Meta-analysis

The initial search strategy retrieved 968 English publications. Of these, 86 articles were selected based on their titles and abstracts, and a full examination of the texts was performed. Seventy-eight papers were excluded since they contained pancreatic head and periampullary malignancies in addition to PDAC. A further 4 studies were excluded due to inadequate statistical data [15–18]. A study evaluating LAPD instead of TLPD for PDAC treatment was also excluded [19]. One study reported the data from the National Cancer Database (NCDB) [20], which compiled cancer registry data in the U.S. and Puerto Rico. Due to the risk of overlapping data with other included studies, this study was also excluded. Finally, only two articles remained [21, 22], each receiving 8 Newcastle–Ottawa (NOS) points. Both articles represent the American experience. A flow chart of the search strategies is illustrated in Fig. 1. Including the present data (after PSM), there were 751 participants in three studies (255 patients in the TLPD group and 496 patients in the OPD group).

The conversion rates of the two included studies were 6.5% (7/108) [21] and 24.1% (14/58) [22], respectively. Although TLPD seemed to have longer durations, the meta-analysis of operative times showed no significant differences between the two groups (WMD = 62.78 min, 95% CI: -17.86 to 143.42, $p = 0.13$; Fig. 3A). However, the intraoperative blood loss was lower in TLPD than in OPD (WMD = -256.94 mL, 95% CI: -461.87 to -52.01, $p = 0.01$; Fig. 3B), as were the transfusion rates (OR = 0.45, 95% CI: 0.32 to 0.66, $p < 0.01$; Fig. 3C). The pooled data further showed shorter lengths of hospital stays with respect to TLPD (WMD = -4.59 days, 95% CI: -6.70 to -2.48, $p < 0.01$; Fig. 3D). In addition, the pooled analysis indicated that the rate of overall morbidity was significantly lower in the TLPD group (OR = 0.51, 95% CI: 0.36 to 0.70, $p < 0.01$; Fig. 3E). Separate analyses were performed by dividing the overall morbidity into major and minor complications according to the Clavien–Dindo classification, in which major complications were graded from III to V and minor ones were graded I and II [23]. We found that both major (OR = 0.55, 95% CI: 0.35 to 0.88, $p = 0.01$; Fig. 3F) and minor complications (OR = 0.66, 95% CI: 0.46 to 0.95, $p < 0.01$; Fig. 3G) were significantly lower in the TLPD group. However, our meta-analysis showed there was no statistically significant difference in mortality (OR = 0.65, 95% CI: 0.21 to 2.06, $p = 0.46$; Fig. 3H) between the two groups. For oncologic outcomes, results showed comparable tumor sizes (WMD = -0.16 cm, 95% CI: -0.53 to 0.21, $p = 0.40$; Fig. 3I). The pooled data of retrieved LNs showed that the number of LNs from TLPD was greater than that of the open group (WMD = 4.19, 95% CI: 0.64 to 7.75, $p = 0.02$; Fig. 3J). Pooling results indicated a comparable R0 rate between the groups (OR = 1.23, 95% CI: 0.82 to 1.86, $p = 0.32$; Fig. 3K). Both studies reported no significant difference in the survival rates between the two groups during their follow-up times. However, quantitative analyses of long-term survival outcomes were not performed due to limited data.

Discussion

Pancreatectomy with lymphadenectomy remains the first-line treatment option for early- and intermediate-stage PDAC. Although laparoscopic DP have become important options for all indications including PDAC on pancreatic bodies and tails [7, 24], approaching PD 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 [5, 8]. This study suggested that TLPD for PDAC were technically feasible and safe. TLPD are longer operations for PDAC treatment than OPD but exhibit clear benefits of less blood loss and shorter hospitalization. More importantly, we found TLPD were associated with lower morbidities than open surgery for PDAC treatments. In addition, laparoscopic procedures appear to hold potential advantages in terms of R0 resections and retrieved LNs. The meta-analysis further confirmed our short-term surgical outcomes. Nevertheless, no statistically significant differences were identified between laparoscopic and open procedures for the treatment of PDAC in the long-term oncological outcomes of recurrence patterns and survival.

The prolonged operative time in TLPD is an obvious disadvantage. Our initial TLPD for PDAC lasted for nearly 600 minutes [14]. Currently, this can be completed in approximately 300–350 minutes [10]. Kendrick et al., in one of the largest single series currently available, described their initial TLPD duration to be 460 min, which improved to 320 min after approximately 50 cases [25]. Stauffer et al., reported a median operative time of 518 min, which was significantly longer than that in open surgery (140 min) [22]. The learning curve can be overcome in high volume centers, with average TLPD operative times decreasing to less than 400 min [26]. However, due to tumor biology and the aggressiveness of the disease process, TLPD for PDAC treatments are not commonly performed making it difficult to overcome the associated learning curve [5]. Although none of studies identified adverse outcomes, 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 [27]. Therefore, we believe long duration is a definite disadvantage of TLPD for PDAC treatments.

In this ITT analysis, the conversion rates were 8.2% (8/98) for all TLPD cases. We found that the conversions generally were due to hemorrhages that were difficult to control or had suspected vessel involvement, which was similar to other publications of TLPD for PDAC treatment [21, 22]. Although there was less overall blood loss, there were still 4 conversions for intraoperative uncontrollable bleeding in this TLPD group. In fact, the multicenter LEOPARD-2 trial was stopped prematurely due to safety concerns of higher mortalities in the LPD group mainly because of intraoperative bleeding [28]. We believe that part of the reason that PDAC frequently induces substantial pancreatic inflammation in the pancreatic remnant is because it is harder to resect due to pronounced adhesions to the surrounding tissues or infiltrations of the portal vein. Portomesenteric vein involvement is a common clinical finding in PDAC, but is a situation that is frequently difficult to diagnose prior to surgery [29]. The rate of venous involvement ranges from 26 to 85% in the literature [30–32]. Portomesenteric vein resection is a means of achieving complete tumor clearance. However, researchers strongly recommend that venous resection during TLPD should only be performed by surgeons with considerable TLPD experience with TLPD and proficiency in open vascular resection [33, 34]. Therefore, approaching appropriate cases like no vessel involvement or severe adhesions laparoscopically in the learning curve would reduce conversion helping to shorten operative time and further reduce bleeding [28].

The most important concern regarding TLPD for PDAC treatments is the patient's safety. We found less postoperative morbidities in TLPD than in OPD (after PSM, 19.1% vs. 33.7%, $p = 0.02$). Furthermore, the meta-analysis indicated not only overall less morbidities in TLPD group, but major and minor complications were also less in the TLPD group when dividing overall complications into major and minor ones according to the Clavien–Dindo classification. POPF is a frequent event and the best management for the pancreatic stump is still under debate with our results revealing no significant differences between the two groups. The anastomoses performed during LPD are the main topic of concern. However, there is no consensus on the best method of anastomosis after PD (e.g., pancreaticojejunostomy or pancreaticogastrostomy, duct-to-mucosa or invagination anastomosis, etc.) [9]. The reported methods in open surgery now can be meticulously performed laparoscopically [5, 35]. No appreciable differences were noted between groups for POPFs because the true risk factors of significant POPFs have been recognized as soft pancreatic parenchyma, high-risk disease pathology, and small pancreatic duct size, rather than the anastomosis method [36, 37]. We argue that the main contributors of lower morbidity in TPLD were reduced delayed gastric emptying (DGE) (after PSM, 5.6% vs. 11.2%, $p = 0.18$) and pulmonary complications (after PSM, 1.1% vs. 5.6%, $p = 0.11$). DGE is not life threatening, but can have significant consequences such as patient discomfort, prolonged hospital stays, increased hospital costs, diminished nutritional status, and delays in initiation of adjuvant therapy [38, 39]. According to the literature, the pathogenesis of DGE is multifactorial and given the improved access and visualization of the laparoscopic approach, as well as the meticulous attention to techniques, potential reasons for this advantage include [40, 41]: 1) laparoscopic surgery has less influence on the peripheral 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. As one of the most complex abdominal surgeries, PD involves multiple systems and would cause more medical complications than other surgeries. It is well known that major abdominal surgery has a detrimental effect on respiratory function, and this is particularly true in upper abdominal surgeries. In general, open procedures are reported to portend a higher risk of pleural effusions, pulmonary infections, and atelectasis than do minimally invasive ones [42, 43].

Oncologic safety and efficacy should be clearly demonstrated prior to a wide application of a new surgical approach. The long-term survival outcomes of MIS for common malignancies have conflicting results [44–46], leading to a constant controversy over MIS for cancer treatments. Oncological surgery requires a radical resection, adequate lymphadenectomy, and meticulous 'no-touch' dissection as it may prevent seeding and tumor cell dissemination. R0 resection is frequently referred to as a crucial factor, which is deemed the only hope for cure [47]. 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 TLPD are comparable to those of open surgery. In addition, our data showed the retrieved LNs of TLPD were not inferior to those of OPD, or even superior to OPD for lymphadenectomy (after PSM, 21.9 ± 6.6 vs. 18.9 ± 5.4 , $p < 0.01$). These findings were further confirmed by the rapid meta-analysis. The advantages of high-resolution imaging, multi-dimensional vision, and meticulous

manipulation help to facilitate lymphadenectomy. A single-center study conducted by Asbun and Stauffer, reported a comparable long-term survival of 1-, 2-, 3-, 4-, and 5-years for OPDs (68, 40, 24, 17, and 15%) and for TLPDs (67, 43, 43, 38, and 32%), respectively [22]. Kuesters et al., conducted a series of LAPD, also reported a comparable 5-year survival rate between LAPD (20%) and OPD (14%) for PDAC [19]. Croome et al., recorded that the progression-free survival was longer in TLPD [21]. In this analysis, we found patients' survival in the TLPD group was superior to those in the OPD group before PSM (RFS: $p = 0.04$, OS: $p = 0.02$). After PSM, in which tumor size and stage were balanced, the 3-year OS and DFS in the TLPD group were still slightly higher than in the OPD group, but the differences failed to reach statistical significance. We believe our results were credible since PSM established the oncologic equivalence of two surgical techniques. We considered there may be other reasons for such results in addition to more LNs examined in the laparoscopic groups. One hypothesis was that improved recovery after laparoscopic surgery helped to instigate multimodality therapies earlier, thus leading to survival benefits [21]. However, a retrospective analysis of the NCDB found that MIS did not improve use or initiation of adjuvant chemotherapy for patients with PDAC [48]. Moreover, the survival impact of the initiation time of adjuvant chemotherapy in patients with resected PDAC remains uncertain since studies showed conflicting results [49, 50]. In our opinion, neither procedure is technically superior, but efficiency would largely depend on the techniques of the surgeon. Thus, considering the principles of radical resection, a technically similar oncologic resection could be performed regardless of whether the an open or laparoscopic approach was used.

Limitations of this study include its retrospective design, small sample size, absence of randomization, and short follow-up period. However, given the fact that TLPD for patients with PDAC are associated with novelty and unpredictable risks, the current study enrolled a relatively large number of cases. To overcome the selection bias arising from a lack of randomization, we performed PSM analyses which was deemed as the most effective method to balance the covariates and thus reduce bias in the retrospective studies.

Conclusions

The current PSM with meta-analysis demonstrated that TLPD for patients with PDAC was a safe alternative to OPD, as it was associated with less blood loss and a better postoperative recovery in terms of a shorter hospital stay and fewer complications. However, this technique also has the disadvantage of longer operative times. Oncological outcomes of TLPD were not inferior to traditional open procedures. Higher levels of evidence including controlled trials are needed to elucidate clear conclusions.

Abbreviations

PDAC: pancreatic ductal adenocarcinoma, TLPD: total laparoscopic pancreaticoduodenectomy, LPD: laparoscopic pancreaticoduodenectomy, OPD: open pancreaticoduodenectomy, DP: distal pancreatectomy, MIS: minimally invasive surgery, LAPD: laparoscopic assisted pancreaticoduodenectomy, PSM: propensity score matching, ITT: intention-to-treat, ISGPF: International

Study Group on Pancreatic Fistula, POPF: postoperative pancreatic fistula, CR-POPF: clinically relevant POPF, RFS: recurrence-free survival, OS: overall survival, PJ: pancreaticojejunostomy, SD: standard deviation, NOS: Newcastle-Ottawa Quality Assessment Scale, OR: odds ratio, WMD: weighted mean difference, CI: confidence interval, NCDB: National Cancer Database, NSQIP: National Surgical Quality Improvement Program, 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, YJF, ZRC, ZMZ, WGY, WXF, and CQL performed the operations; PY, HCJ and CQL reviewed the medical records and collected data; MYP and CQL proofread and revised the manuscript; all authors read and approved the final manuscript.

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Figures

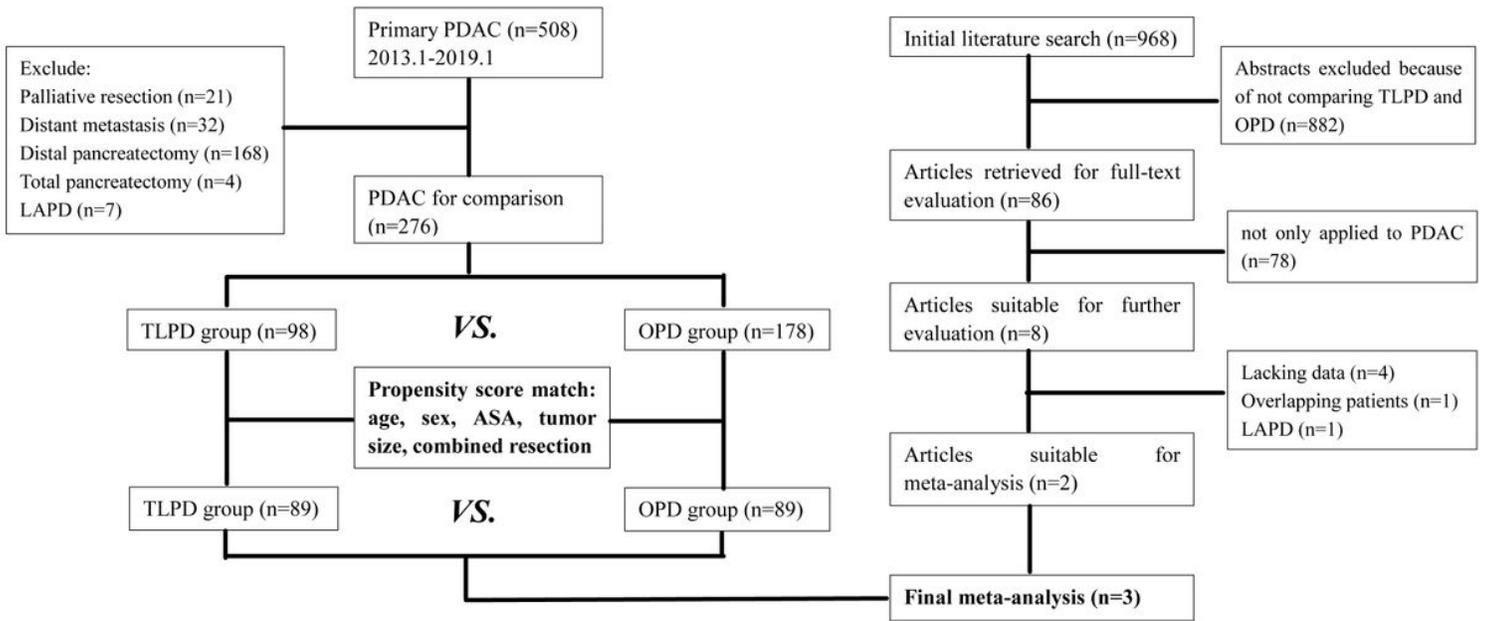


Figure 1

Flow chart of patient selection and literature search strategy.

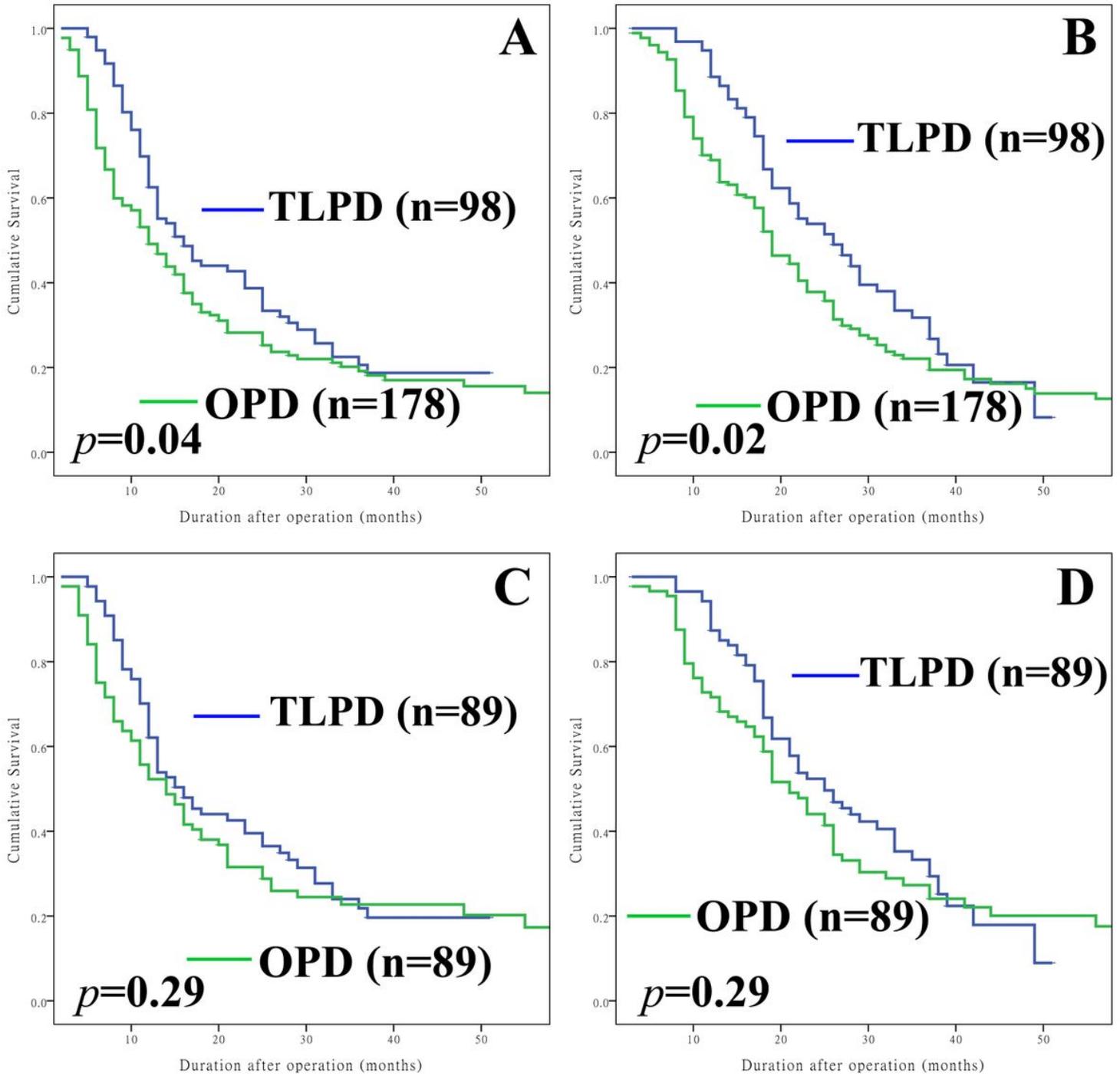


Figure 2

Kaplan-Meier survival curves of TLPD vs. OPD for PDAC treatment. (A) Cumulative RFS before matching. (B) Cumulative OS before matching. (C) Cumulative RFS after matching. (D) Cumulative OS after matching. RFS: recurrence-free survival, OS: overall survival.

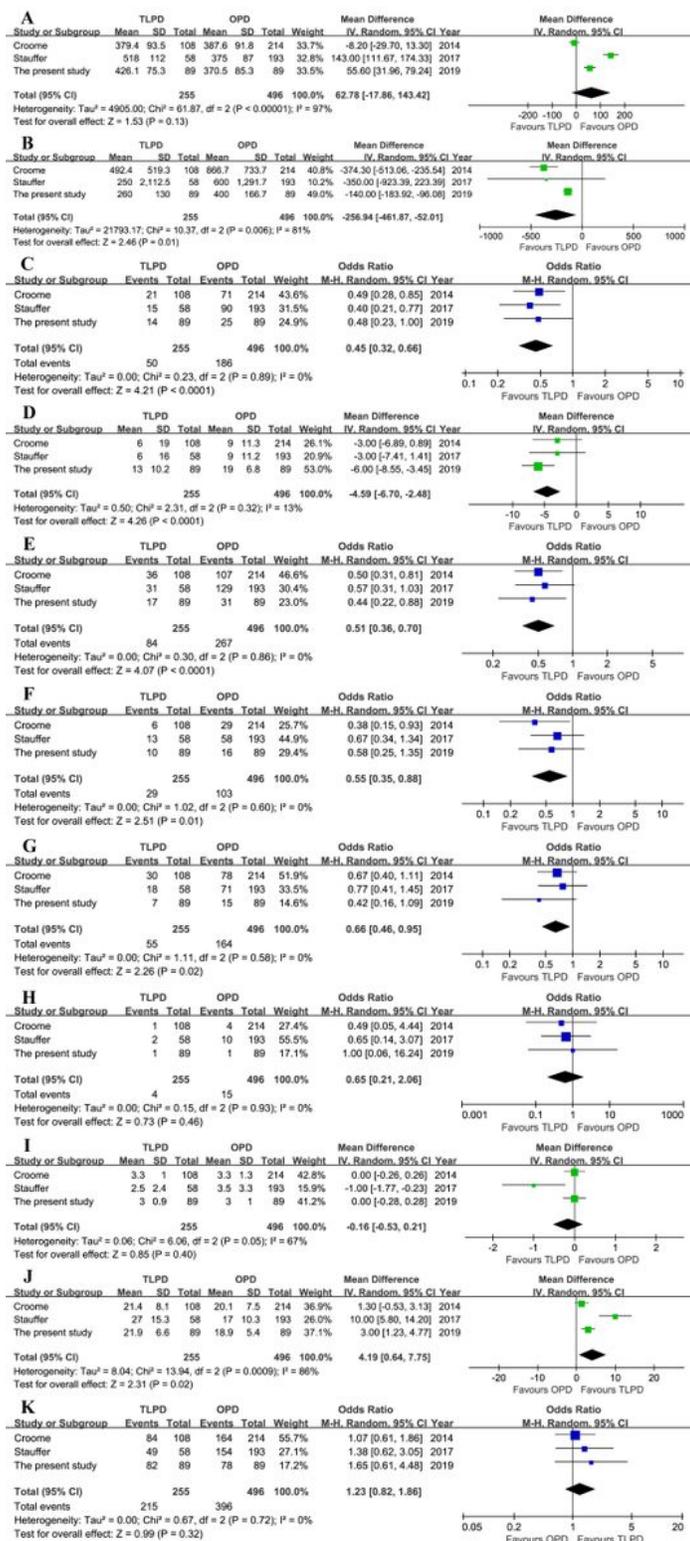


Figure 3

Meta-analysis of the pooled data. (A) Operative time. (B) Blood loss. (C) Transfusion. (D) Hospital stay. (E) Morbidity. (F) Major complications. (G) minor complications. (H) Mortality. (I) Tumor size. (J) Retrieved lymph nodes. (K) R0 rate.

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