Comparison of Laparoscopic and Open Pancreatoduodenectomy for the Treatment of Nonpancreatic Periampullary Adenocarcinomas

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Background: Laparoscopic pancreatoduodenectomy (LPD), a surgical option for nonpancreatic periampullary adenocarcinoma (NPPA), is a complex procedure that has become increasing popular. However, there is no consensus as to whether this technique should be performed routinely. Our aim was to evaluate the outcomes of LPD compared with open pancreatoduodenectomy (OPD).

Materials and Methods: From October 2010 to September 2015, 58 LPDs were performed to treat NPPA and were compared with 58 OPDs, which can theoretically be carried out by laparoscopic approach. Patients were also matched based on their demographic data and pathologic diagnosis. Demographic information, intraoperative and postoperative data, pathologic data, and follow-up evaluation data were collected at our center.

Results: All patients had a median follow-up of 34 months (range, 8 to 60). Overall median survival during the study between the groups was not different (P = 0.760). No significant differences between the 2 groups were found in terms of patient demographics, short-term complications, pathologic outcomes, or tumor-node-metastasis stage. With regard to operative time, the LPD group was slightly longer than the OPD group (P < 0.001). There were significant differences between groups in the time to the first passage of flatus and the time to oral intake (P < 0.001). However, no differences were seen in blood loss, length of intensive care unit stay, node positive, or R0 resection between the laparoscopic and open groups.

Conclusions: This study found that LPD is a feasible, safe, and effective method for the treatment of NPPA compared with OPD and may be a preferred method for surgeons to choose.

Key Words: nonpancreatic periampullary adenocarcinomas, laparoscopic pancreatoduodenectomy, feasibility, survival

(Surg Laparosc Endosc Percutan Tech 2018;28:56–61)

MPULLARY adenocarcinoma is a rare malignancy that accounts for 7% of all periampullary cancers.1 Primary adenocarcinomas arising from the pancreatic head, distal common bile duct, ampulla, and periampullary duodenum are often misdiagnosed as periampullary carcinomas. Preoperatively, it is difficult to identify primary ampullary cancers from other periampullary cancers.2 Moreover, ampullary adenocarcinoma originating from the pancreas has a completely distinct 5-year survival. Nonpancreatic periampullary adenocarcinoma (NPPA) includes distal common bile duct, ampulla, and periampullary duodenum tumors. So, it is necessary to distinguish ampullary adenocarcinoma originating from the pancreas from other ampullary adenocarcinoma.

Pancreatoduodenectomy (PD) is the only potential cure for NPPA patients, almost 50% of ampullary cancer patients undergo surgical resection.3 Currently, minimal invasive surgery has rapidly evolved to pancreatic surgical procedures. Some studies have demonstrated that laparoscopic pancreatoduodenectomy (LPD) was better than open pancreatoduodenectomy (OPD).4,6 However, Dokmak et al7 reported that LPD is a difficult procedure and has high morbidity. They concluded that LPD should not be routine for resection of periampullary tumors. Therefore, we conducted this study to assess the safety and feasibility of LPD in the treatment of NPPA.

MATERIALS AND METHODS

Patient Selection

From October 2010 to September 2015, 58 consecutive LPD procedures for patients with NPPA were performed at the Department of Pancreatic Surgery, West China Hospital, Sichuan University, China. In addition, 58 patients who underwent OPD were selected from our center. These patients were matched with patients who underwent LPD based on their demographic data (mainly age and sex) and pathologic diagnosis.

To reduce selection bias and enhance the comparison between groups, the patients who underwent OPD all could have had a laparoscopic procedure. We followed the methods of our previous article.5 The selection criteria for standard LPD or OPD included the following: (1) body mass index <28.0 kg/m²; (2) ampullary tumors, duodenal tumors restricted to the second part of the duodenum, or lower common bile duct tumors; and (3) carefully confirmed resectability of the tumors based on preoperative radiology conducted by experienced radiologists and surgeons. Patients with >180 degrees superior mesenteric artery encasement, any celiac abutment, unreconstructable superior mesenteric vein/portal occlusion, aortic invasion or encasement, a history of previous upper abdominal surgery, tumors extending to the uncinate, and severe cardiorespiratory issues were not included in the study.
comorbidities, were excluded from undergoing LPD. More importantly, the final decision on whether to perform an OPD or an LPD was left to the discretion of the surgeon and the patient.

All the patients were thoroughly informed about the procedure, risks, and the advantages of LPD and OPD. Written informed consent was obtained from all the patients in our study, which was approved by the ethics committee of Sichuan University.

Data Collection

The data were prospectively collected and entered into a database for analysis and included the following preoperative, intraoperative, and postoperative variables. Operative time was defined as the duration of time from the first incision to the final closure. Estimated blood loss was measured by the weight of the swabs plus the blood removed during the procedure. The surgeon assessed the pancreatic texture (soft vs. firm) according to the margins of the resected specimen. The pancreatic duct width (≤3 or >3 mm) was measured from preoperative computed tomography/ magnetic resonance imaging anteroposteriorly at the level at which the portal vein passes posterior to the pancreatic neck. Demand for analgesia indicated that postoperative patient-controlled analgesia, 250 μg of fentanyl diluted to 200 mL in normal saline, was initiated when the patients were unable to tolerate postoperative pain within 24 hours after the LPD.

Definitions

The postoperative stay was defined as the interval from surgery to the day of discharge. For tumor cases, the final pathologic results were recorded according to tumor-node-metastasis (TNM) staging, histologic grade of differentiation, total number of harvested lymph nodes, resection margin status, lymph node invasion status, and mass size based on the AJCC Cancer Staging Manual, Seventh Edition.9 R0 resection indicated that no evidence of malignancy was identified at any of the resection margins, and R1 resection was defined as malignancy infiltrating at least one of the resection margins on a permanent section. Short-term complications, which were stratified by the Clavien-Dindo classification of surgical complications, indicated morbidities within 30 postoperative days.10 Postoperative pancreatic fistula (POPF), delayed gastric emptying (DGE), and postpancreatectomy hemorrhage (PPH) were defined according to the International Study Group (ISGPs).11-14 Reoperation was defined as a secondary operation due to severe complications within 30 days following LPD. The patients were discharged when oral intake and moderate activity were tolerated without any abnormal postoperative complications or laboratory findings.

Statistical Analyses

For quantitative data, the results were expressed as the mean ± SD. The median with interquartile range was used for skewed quantitative data. For categorical data, the results were expressed as the number and percentage of cases. Values are expressed as the means and ranges, or percentages, when appropriate. The χ2 test was used to compare categorical variables. The independent t test and the rank sum test were used to compare continuous variables. Survival of nonperipancreatic carcinoma patients was calculated using the Kaplan-Meier method, rank sum test, and Cox regression analysis. All statistical analyses were performed using SPSS 16.0 statistical software (SPSS Inc., Chicago, IL). The level for rejection of the null hypothesis was set at a P-value of <0.05.

RESULTS

Patient Characteristics

In total, 58 patients who underwent LPD and 58 patients who underwent OPD from October 2010 to September 2015 were identified. All patients had a median of 34 months of follow-up (range, 8 to 60 mo). Demographics of NPPA patients are shown in Table 1. The mean age of the patients was 59.95 ± 9.12 years in the LPD group and 60.33 ± 8.66 years in the OPD group. The proportion of male patients was 55.17% in the LPD group and 58.62% in the OPD group (P = 0.708). In total, 62 (53.4%) patients in the LPD group and 54 (46.6%) patients in the OPD group were classified as American Society of Anesthesiology (ASA) II and III, respectively. Jaundice and epigastric pain were the predominant initial symptoms. There was no difference in tumor biomarkers including carbohydrate antigen 19-9 (CA 19-9), carbohydrate antigen 125 (CA125), and carcinoembryonic antigen between the 2 groups.

Operative Data

The operative time was longer in the LPD group (475.0 min, 420.0 to 546.3 min vs. 335.0 min, 275.0 to 405.0 min; P < 0.001), but there was no difference in blood loss or transfusion rate (Table 2). There were no significant differences in postoperative intensive care unit utility, length of postoperative stay, or pancreatic texture. However, the LPD group showed faster time to oral intake and time to first passage of flatus, as well as demand for analgesia (P < 0.001) compared with the OPD group.

Short-term Complications

The short-term postoperative surgical complications, including POPF, PPH, DGE, and pulmonary infection, were not significantly different between the 2 groups. The most common complication was POPF, and the occurrence rates were 55.17% and 58.62% in the LPD group and the OPD group, respectively. Grade A POPF accounted for 75% and 76% of POPF complications in each group and grades B and C POPF were more clinically relevant complications that required clinical intervention. Grade B POPF was the most common grade I to II postoperative complication, occurring in 8 patients (14.0%), and grade B DGE was the second-most common, occurring in 4 patients (7.0%). On the basis of the Clavien-Dindo classification, there were 9 cases (15.52%) of grades III to IV postoperative complications in the 2 groups, respectively. There were no significant differences in severe postoperative complications (grade ≥III) between the 2 groups, which occurred in 9 patients (15.52%). All the patients with grade ≥III postoperative complications required surgical or endoscopic interventions. All postoperative complications are described in detail in Table 3.

The 30-day mortality was one (1.72%) in each group. The reoperation rates were 6.90% and 5.17% in the LPD group and the OPD group, respectively. One death occurred on postoperative day 14 in a patient who underwent LPD for T3N1M0 CBD. Overall, severe complications were not significantly different between the 2 groups. Although the differences were not significant for abdominal infection (5.17% vs. 1.72%, P = 0.464), there was a tendency toward fewer occurrences in the LPD group. And, there was no
TABLE 1. Demographics of NPPA Patients

| Parameters                      | LPD (n = 58)       | OPD (n = 58)       | P     |
|--------------------------------|-------------------|-------------------|-------|
| Age (y)                        | 59.95 ± 9.12*     | 60.33 ± 8.66*     | 0.819†|
| Sex (male/female)              | 32/26             | 34/24             |       |
| BMI (kg/m²)                    | 22.27 ± 2.96*     | 22.95 ± 2.34*     | 0.172‡|
| ASA (II/III) [n/N (%)]          | 28 (48.28)/30 (51.72) | 34 (58.62)/24 (41.38) | 0.264‡|
| Preoperative CA 9-9 (U/mL)      | 95.29 (28.29-317.58) | 77.32 (15.46-226.9) | 0.186‖|
| Preoperative CEA (ng/mL)        | 3.13 (1.23-3.94)  | 1.94 (1.35-2.72)  | 0.116‖|
| Preoperative CA125 (ng/mL)      | 11.92 (8.08-22.31) | 13.63 (8.89-22.04) | 0.563‡|
| Preoperative total bilirubin (mmol/L) | 68.45 (22.85-161.62) | 51.55 (14.23-201.72) | 0.447‡|
| Preoperative direct bilirubin (mmol/L) | 63.95 (15.45-144.58) | 41.70 (8.30-185.38) | 0.416‡|
| ENBD or PTCD [n (%)]           | 26 (44.83)        | 18 (31.03)        | 0.126‡|
| Pancreatic duct width [n (%)]  | 3 mm              | 3 mm              |       |
| Jaundice with/without pruritus  | 14 (24.14)        | 15 (25.86)        | 0.830‡|
| Jaundice with/without pruritus + Epigastric pain | 15 (25.86) | 12 (20.69) | 0.510‡|
| Jaundice with/without pruritus + Epigastric pain | 28 (48.28) | 28 (48.28) | 1.000‡|
| Others                         | 1 (1.72)          | 3 (5.17)          | 0.309‡|
| Comorbidities [n (%)]          |                   |                   |       |
| Chronic bronchitis             | 4 (6.90)          | 1 (1.72)          | 0.170‡|
| Chronic gastritis or duodenitis| 2 (3.45)          | 4 (6.90)          | 0.402‡|
| Hypertension                   | 9 (15.52)         | 6 (10.34)         | 0.406‡|
| Diabetes                       | 4 (6.90)          | 6 (10.34)         | 0.508‡|
| Chronic anemia                 | 3 (5.17)          | 1 (1.72)          | 0.309‡|

*Data are expressed as mean ± SD.
†Independent t test.
‡The χ² test.
§Data are expressed as median and interquartile range.
‖Rank sum test.

ASA indicates American Society of Anesthesiology; BMI, body mass index; CA 19-9, carbohydrate antigen 19-9; CA125, carbohydrate antigen 125; CEA, carcinoembryonic antigen; ENBD, endoscopic nasal biliary drainage; LPD, laparoscopic pancreaticoduodenectomy; NPPA, nonpancreatic peripancreatic adenocarcinoma; OPD, open pancreaticoduodenectomy; PTCD, percutaneous transhepatic cholangial drainage.

TABLE 2. Intraoperative and Postoperative Data Among the LPD and OPD

| Variables                      | LPD               | OPD               | P     |
|--------------------------------|-------------------|-------------------|-------|
| Operative time (min)           | 475.0 (420.0-546.3)* | 335.0 (275.0-405.0)* | <0.001†|
| Intraoperative transfusion [n (%)] | 11 (18.97)       | 9 (15.52)         | 0.623‡|
| Estimated blood loss (mL)      | 200.0 (100.0-325.0)* | 220.0 (150.0-400.0)* | 0.334‡|
| Pancreas texture (soft) [n (%)] | 28 (48.28)        | 26 (44.83)        | 0.710†|
| Postoperative ICU utility [n (%)] | 9 (15.52)        | 7 (12.07)         | 0.590‡|
| Demand for analgesia [n (%)]   | 26 (44.83)        | 54 (93.10)        | <0.001†|
| Postoperative stay (d)         | 14.0 (11.0-17.3)* | 13.0 (11.0-20.0)* | 0.608‡|
| Time to first passage of flatus (d) | 4.0 (3.0-5.0)* | 5.0 (4.0-5.0)* | <0.001†|
| Time to oral intake (d)        | 6.0 (5.0-8.0)*    | 7.0 (6.0-11.0)*   | <0.001†|

*Data are expressed as median and interquartile range.
†Rank sum test.
‡The χ² test.
ICU indicates intensive care unit; LPD, laparoscopic pancreaticoduodenectomy; OPD, open pancreaticoduodenectomy.

With regard to final pathologic outcomes, distal common bile duct cancer was identified in 29 cases (LPD, 16 cases vs. OPD, 13 cases), duodenal papillary adenocarcinoma in 69 cases (LPD, 34 cases vs. OPD, 35 cases), and ampullary adenocarcinoma in 18 cases (LPD, 8 cases vs. OPD, 10 cases). As the staging parameters for different malignancies vary, TNM staging and tumor differentiation were confirmed for each individual case according to the AJCC Cancer Staging Manual, Seventh Edition. No significant differences were observed in tumor size between the 2 groups (P = 0.079). There were no differences between groups in the tumor size (P = 0.079), number of harvested lymph nodes [16 (15 to 18) vs. 15 (15 to 17), P = 0.085], number of invaded lymph nodes [10 (17.24%) vs. 12
TABLE 3. Short-term Complications and Surgical Outcomes Compared by Operative Method

| Variables          | LPD     | OPD     | P      |
|--------------------|---------|---------|--------|
| POPF               | 32 (55.17) | 34 (58.62) | 0.708* |
| Grade A            | 24 (41.38) | 26 (44.83) | 0.708* |
| Grade B            | 7 (12.07) | 7 (12.07) | 1.000* |
| Grade C            | 1 (1.72) | 1 (1.72) | 1.000* |
| PPH                | 5 (8.62) | 5 (8.62) | 1.000* |
| Grade A            | 1 (1.72) | 2 (3.45) | 0.559* |
| Grade B            | 2 (3.45) | 2 (3.45) | 1.000* |
| Grade C            | 2 (3.45) | 1 (1.72) | 0.559* |
| DGE                | 9 (15.52) | 9 (15.52) | 1.000* |
| Biliary fistula    | 2 (3.45) | 2 (3.45) | 1.000* |
| Gastroenteric anastomosis fistula | 1 (1.72) | 3 (5.17) | 0.309* |
| Pulmonary infection| 6 (10.34) | 7 (12.07) | 0.769* |
| Chylos leakage     | 5 (8.62) | 2 (3.45) | 0.242* |
| Abdominal infection| 8 (13.79) | 9 (15.52) | 0.793* |
| Afferent loop obstruction | 1 (1.72) | 0 (0.00) | 1.000† |
| Abdominal abscess  | 3 (5.17) | 5 (8.62) | 0.464* |
| Clavien ≥ III      | 9 (15.52) | 9 (15.52) | 1.000* |
| Reoperation        | 4 (6.90) | 3 (5.17) | 0.697* |
| 30-day mortality   | 1 (1.72) | 1 (1.72) | 1.000* |

*The χ² test.
†The Fisher exact test.
‡The Fisher exact test.

The χ² test.
†Data are expressed as median and interquartile range.
‡Rank sum test.
§The Fisher exact test.

TABLE 4. Pathologic Outcomes and TNM Stage Among the 2 Groups Patients

| Outcomes                  | LPD     | OPD     | P      |
|---------------------------|---------|---------|--------|
| TNM staging               |         |         |        |
| T0N0M0                    | 0       | 0       | NA     |
| T1N0M0                    | 1       | 3       | 0.611* |
| T2N0M0                    | 29      | 24      | 0.351* |
| T3N0M0                    | 17      | 17      | 1.000* |
| T3N1M0                    | 11      | 11      | 0.623* |
| T4N0M0                    | 1       | 2       | 1.000* |
| T4N1M0                    | 1       | 1       | 1.000* |
| Tumor differentiation     |         |         |        |
| Well                      | 6       | 6       | 1.000* |
| Poorly to moderately      | 42      | 42      | 1.000* |
| Tumor size (cm)           | 1.85    | 2.00    | 0.079† |
| (1.50-2.60)†              | (1.95-3.00)† |        |
| No. lymph nodes collected | 16 (15-18)† | 15 (15-17)† | 0.085‡ |
| Node positive [n (%)]     | 10 (17.24) | 12 (20.69) | 0.636* |
| R0 resection [n (%)]      | 58 (100.0) | 55 (94.83) | 0.243§ |

*The χ² test.
†Data are expressed as median and interquartile range.
‡Rank sum test.
§The Fisher exact test.

The χ² test.
†Data are expressed as median and interquartile range.
‡Rank sum test.
§The Fisher exact test.

The LDG group to have more harvested lymph nodes than the OPD group [16 (15 to 18) vs. 15 (15 to 17)]. All the final pathologic information is shown in Table 4.

All patients had a median follow-up of 34 months (range, 8 to 60 mo). Overall median survival during the study between the groups was not different (LPD, 45 mo vs. OPD, 48 mo; P = 0.760) (Fig. 1A). No significant differences concerning median survival were noted when the 3 pathologic types were compared (distal common bile duct cancer, 50 mo; duodenal papillary adenocarcinoma, 45 mo; ampullary adenocarcinoma, 40 mo; P = 0.990) (Fig. 1B).

DISCUSSION

PD is the only potential cure for pancreatic periampullary adenocarcinomas. However, the benefits of the LPD are still debated. Asbun and Stauffer reported that LPD is safe and feasible compared with OPD. Palaniavel et al also had similar results. However, Dokmak et al reported that LPD had higher morbidity and should be performed in only the patients with a low risk of PF. This was a retrospective study conducted over a median of 34 months (range, 8 to 60 mo) comparing 2 different methods for PD. The analysis focused on long-term results with regard to operative time, postoperative complications, and survival.

In our study, we found that LPD and OPD had similar outcomes with regard to patient demographics. Preoperatively, jaundice and abdominal pain were the main symptoms in patients with NPPA. There were 29 patients (25%) presenting with jaundice (14 in the LPD group, 15 in the OPD group). Preoperative mean total bilirubin was not significantly different between the 2 groups [68.45 (22.85 to 161.62) vs. 51.55 (14.23 to 201.72); P = 0.447]. Percutaneous transhepatic cholangial drainage was performed in 44 patients (37.9%).

For NPPA patients, LPD is as feasible, safe, and effective as OPD. Croome et al reported 89 patients with major vascular resection undergoing total laparoscopic pancreaticoduodenectomy (n = 31) and OPD (n = 58). There were significant differences in the mean operative blood loss (842 vs. 1452 mL, P < 0.001) and median hospital stay (6 vs. 9 d, P = 0.006). There were no significant differences in the operative times and complications. In contrast, previous studies have shown that operative times were substantially longer than OPD. In our center, the mean operative time was longer in the LPD group [475.0 min (420.0 to 546.3 min) vs. 335.0 min (275.0 to 405.0 min); P < 0.001]. Compared with patients who underwent OPD, patients who underwent LPD had a shorter time to first passage of flatus and oral intake (P < 0.001).

POPF, DGE, and PPH were common complications. POPF occurred in 66 patients (32 in the LPD group and 34 in the OPD group; P = 0.708). Grade C pancreatic fistula occurred in 2 patients. There was also no significant difference in the rates of occurrence of DGE and PPH. There were 7 cases of reoperation due to PPH or wound infection. In addition, 1 death occurred in the LPD group secondary to PPH, and 1 death occurred in the OPD group secondary to a grade C pancreatic fistula. In our study, we found that there were no significant differences in short-term complications between the 2 groups. However, Dokmak et al reported that LPD had a higher morbidity. They found that grade C pancreatic fistulas (P = 0.007) and bleeding (P = 0.02) were significantly different between groups. Therefore, they concluded that LPD is not suitable due to the high risk of pancreatic fistula.
Because of the complex anastomoses and substantial dissection around major blood vessels, LPD is a difficult procedure for surgeons to perform. Yet, Al-Taan et al.\(^1^9\) felt that though LPD is a time-consuming procedure, it can be safely performed by experienced surgeons. Currently, the operative time for LPD varied widely, ranging from 342 to 541 minutes.\(^7\)\(^{15,20-22}\) Interestingly, in our previous study, the operative time for LPD was 515 minutes.\(^23\) However, the operative time was reduced to 475 minutes in the current study. More importantly, the short-term complications seemed to be decreased compared with previous procedures. In our previous study, we found that the learning curve was associated with decreased operative time, blood loss, and postoperative intensive care unit demand.\(^8\) Therefore, although LPD is a complex surgical procedure, one that pancreatic surgeons have been slow to adopt, LPD has more benefits than OPD.

Taken together, the data of the present study show that surgical resection is the only potential cure for NPPA.\(^1^8\) There is currently no consensus as to whether different surgical
procedures result in different outcomes. Croome et al.\(^7\) reported no significant difference in overall survival between the LPD and OPD groups (\(P = 0.22\)), R0 resection (\(P = 0.038\)) and the mean number of involved lymph nodes (\(P = 0.01\)) both had a higher rate in the LPD group compared with the OPD group. Similarly, Asbun and Stauffer\(^5\) reported that there were significant differences in the number of lymph nodes excised (\(P = 0.007\)) and the lymph node ratio (\(P < 0.001\)) between the 2 groups. However, another study had different view. Chalikonda et al.\(^6\) had found that robotic PD had a higher R0 rate and an increased number of lymph nodes excised. However, in our study, R0 resection occurred in all the LPD patients, and only 3 cases were R1 resection in the OPD group. In addition, there was no significant difference with regard to the survival between the 2 groups (\(P = 0.760\)). One of the possible reasons for our conclusion is that after a long learning curve, laparoscopic surgeons attained technical competence, which may have reduced the operative time and blood loss and decreased the R1 rate and number of lymph nodes retrieved.

It can be argued that this study had limitations, including a small number of patients, data from only a single center, and a not very long follow-up. Thus, more studies from multiple centers are needed to support our conclusions. In conclusion, based on this study, LPD was associated with equivalent short- and long-term outcomes compared with OPD, and LPD is a feasible, safe, and effective method for the treatment of NPPA and may be a preferred method for surgeons to choose.

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