Hepatopancreatoduodenectomy for advanced biliary malignancies

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Abstract

Background: Hepatopancreatoduodenectomy (HPD) has been considered the only curative treatment for metastatic cholangiocarcinoma and some locally advanced gallbladder cancers (GBCs). However, HPD has not yet been included in treatment guidelines as a standard surgical procedure in consideration of its morbidity and mortality rates. The aim of this study was to evaluate the safety and effectiveness of HPD in treating biliary malignancies.

Methods: The medical records of 57 patients with advanced biliary cancer undergoing HPD from January 2009 to December 2019 were retrospectively retrieved. A case-control analysis was conducted at our department. Patients with advanced GBC who underwent HPD (HPD-GBC group) were compared with a control group (None-HPD-GBC group). Baseline characteristics, preoperative treatments, tumor pathologic features, operative results, and prognosis were assessed.

Results: Thirteen patients with cholangiocarcinoma and 44 patients with GBC underwent HPD at our department. Significant postoperative complications (grade III or greater) and postoperative pancreatic fistula were observed in 24 (42.1%) and 15 (26.3%) patients, respectively. One postoperative death occurred in the present study. Overall survival (OS) was longer in patients with advanced cholangiocarcinoma than in those with GBC (median survival time [MST], 31 months *vs*. 11 months; $P < 0.001$). In the subgroup analysis of patients with advanced GBC, multivariate analysis demonstrated that T4 stage tumors ($P = 0.012$), N2 tumors ($P = 0.001$), and positive margin status ($P = 0.004$) were independently associated with poorer OS. Patients with either one or more prognostic factors exhibited a shorter MST than patients without those prognostic factors ($P < 0.001$).

Conclusion: HPD could be performed with a relatively low mortality rate and an acceptable morbidity rate in an experienced high-volume center. For patients with advanced GBC without an N2 or T4 tumor, HPD can be a preferable treatment option.

Keywords: Hepatectomy; Hepatopancreatoduodenectomy; Gallbladder cancer; Cholangiocarcinoma

Introduction

Hepatopancreatoduodenectomy (HPD) is the combination of hepatectomy and pancreatoduodenectomy (PD). It was first introduced by Takasaki *et al*[1] for the radical resection of locally advanced gallbladder cancer (GBC) in 1980. HPD theoretically offers the opportunity to cure patients with cholangiocarcinoma with extensive ductal spread invading from the hepatic hilum to the intrapancreatic bile duct or GBC with lower biliary and peripancreatic infiltration and lymph node involvement. However, this procedure remains controversial because of the unsatisfactory long-term benefits and high morbidity and mortality rates according to different reports.[2-7] During the last few decades, with not only the refinements in perioperative management and surgical techniques but also the advancement of our understanding of the anatomies of the hepatobiliary system and the pancreatoduodenal region, the mortality rate of HPD has gradually decreased.[8]

In the present study, the short- and long-term outcomes of 57 consecutive patients with advanced biliary cancer who underwent HPD were retrospectively analyzed. The aim of

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this study was to review our experience with this difficult procedure to identify prognostic factors that affect long-term outcomes.

Methods

Ethical approval

This study complied with the *Declaration* of *Helsinki* and completely adhered to the current ethical guidelines. Ethical approval was obtained from the Ethics Committee of Xinhua Hospital, Shanghai Jiao Tong University School of Medicine (2020–084).

Study population

Fifty-seven patients with advanced biliary cancer who underwent HPD with curative intent at our department from January 2009 to December 2019 were retrospectively studied. R0 or R1 resections were defined as resection with curative intent.[9] Patients' clinicopathological characteristics, laboratory indices, and perioperative treatment were retrieved from a retrospective review of medical records.

Moreover, a case-control analysis was conducted at our department. Patients with advanced GBC who underwent HPD (HPD-GBC group) were compared with a control group (None-HPD-GBC group). Cases of the HPD-GBC group were matched at a 1:1 ratio based on primary tumor and nodular stage, age, gender, and body mass index (BMI) with the None-HPD-GBC group. The None-HPD-GBC group included patients who underwent radical cholecystectomy without PD.

Preoperative management

Contrast-enhanced computed tomography (CT) was routinely employed for preoperative tumor staging. Magnetic resonance imaging and magnetic resonance cholangiopancreatography were utilized when the patient had obstructive jaundice. Positron emission tomography was applied in selected patients suspicious for distant metastasis. Endoscopic or percutaneous transhepatic biliary drainage was carried out if the total bilirubin level was >17.5 mg/dL or if acute cholangitis occurred. For patients with an estimated liver volume of hepatectomy reaching 70% or more, portal vein embolization (PVE) was indicated and performed when the total bilirubin level was <3 mg/dL. An indocyanine green retention rate of 15% at 15 min after intravenous injection was deemed acceptable for major hepatectomy.

Surgical strategy

HPD was preferred for GBC patients under the following conditions: diffuse bile duct infiltration with involvement of the intrapancreatic bile duct; direct invasion into the duodenum not amenable to partial duodenectomy to achieve R0 resection; infiltration of the pancreatic parenchyma at the pancreatic head; and/or bulky lymph node metastasis invading the pancreatic head. For cholangiocarcinoma, HPD was considered when (1) an infiltrating tumor diffusely spread across the whole extrahepatic bile duct, (2) a perihilar tumor exhibited bulky nodal metastasis within the pancreatoduodenal region, (3) a perihilar tumor exhibited downward superficial infiltration, or (4) a distal tumor exhibited upward superficial infiltration. Macroscopically involved adjacent organs, such as the colon and stomach, and/or vascular structures, including the portal vein, were resected en bloc with the main tumor.

After ruling out intra-abdominal metastasis by laparoscopy or laparotomy, Kocher's maneuver was applied to lift the head of the pancreas and the duodenum, and biopsy of the periaortic lymph node was routinely performed. Radical surgery was abandoned if a positive periaortic lymph node was confirmed. Normally, HPD is performed in the following order to achieve en bloc resection. First, the pancreas and jejunum are segmented according to the PD method, and the small vessels between the uncinate process and the superior mesenteric artery are ligated. Second, the lymph nodes in the hepatoduodenal ligament are cleaned according to the vascular system. Third, the liver is transected after ligating the corresponding portal vein and hepatic artery according to the scope of hepatectomy.

Major hepatectomy was defined as hepatectomy procedures resecting three or more sections. Liver transection was mainly performed with the "curettage and aspiration dissection technique" by Peng's multifunctional operative dissector[10] under hepatic inflow clamping for 10 min with 3-min intervals [Figure 1]. Vascular resection was performed based on the preoperative CT scan and the intraoperative confirmation of macroscopic vascular invasion. For reconstruction, a modified Child's method was routinely applied. An end-to-side, duct-to-mucosa, two-layer pancreaticojejunostomy was constructed using continuous fine Prolene sutures. Internal pancreatic stenting was employed routinely. The choledochojejunos-tomy was conducted by continuous fine absorbable sutures in an end-to-side, duct-to-mucosa, one-layer way.

Postoperative management and adjuvant treatment

Postoperative complications, including posthepatectomy liver failure,[11] bile leakage,[12] and postoperative pancreatic fistula (POPF),[13] were classified according to standard definitions.[14] Blood tests of complete blood count, liver function, and renal function were measured on days 1, 3, 6, and 9 after surgery. Total bilirubin and amylase concentrations in the abdominal drain fluid were measured on days 3 and 7 to distinguish postoperative bile leakage and/or POPF. An abdominal CT scan was performed on day 7 to identify abnormal intra-abdominal fluid collections. The drainage tube(s) were exchanged or adjusted to a proper position under fistulography, if necessary. Additional drainage was employed under the guidance of ultrasound if the abdominal fluid collection was detected as suspicious of an abscess.

The final disease staging and histological grading were determined according to the 8th edition of the American Joint Committee on Cancer (AJCC) staging system.[15] Thirty-four of the 57 patients received gemcitabine plus

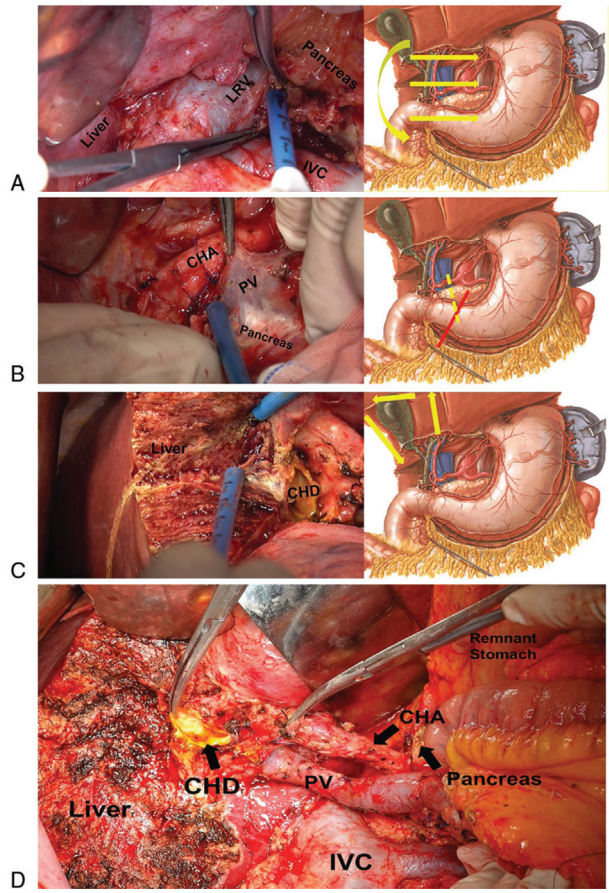

Figure 1: Intraoperative image and diagram demonstrating en bloc resection of segment 4a + 5 and PD. (A) Kocher's maneuver was applied to the lift head of the pancreas and the duodenum, and a biopsy of the periaortic lymph node was routinely performed. (B) PD: after transecting the gastric antrum, the pancreas, and the jejunum, the small blood vessels between the uncinate process and the SMA were separated and ligated until its root. The red solid line indicates the transection of the gastric antrum. The yellow dotted line indicates the transection of the pancreas at the neck. (C) Resection of segment 4a + 5. (D) After the completion of segment 4a + 5 resection and PD. CHA: Common hepatic artery; CHD: Common hepatic duct; IVC: Inferior vena cava; LRV: Left renal vein; PD: Pancreatoduo-denectomy; PV: Portal vein; SMA: Superior mesenteric artery.

oxaliplatin as postoperative adjuvant chemotherapy according to their tumor-node-metastasis (TNM) stage or residual disease status. For patients with relapsed disease, gemcitabine plus oxaliplatin was employed as a first-line treatment.

All the patients were carefully monitored. Blood tests of tumor markers and ultrasound or CT imaging were conducted every 3 months. The follow-up period started at the date of the initial diagnosis of biliary cancer and ended at the last follow-up visit (December 2019) or death. None of the patients were censored due to loss of follow-up.

Statistical analysis

Categorical variables are presented as numbers and percentages, and continuous variables are presented as medians and ranges. Continuous variables were compared using the Mann – Whitney *U* test, and categorical variables were compared using the χ^2 test. Overall survival (OS) was estimated by the Kaplan–Meier method and compared using the log-rank test. Univariate analysis was carried out to determine the prognostic factors. Factors with a *P* value <0.05 were included in multivariate analysis using Cox proportional hazards regression.

All tests were two-sided, and *P* values of <0.05 were considered statistically significant. All statistical analyses were performed using the statistical software SPSS for Windows, Version 19.0 (IBM Corp., Armonk, NY, USA).

Results

Patient and tumor characteristics

Clinicopathological features are summarized in Table 1 (bile duct and gallbladder, 13 *vs.* 44). No significant differences were observed for age, sex, BMI, or preoperative levels of tumor markers. Preoperative biliary drainage and preoperative PVE were more frequently performed in patients with bile duct carcinoma, and there was no difference between the groups. The types of hepatic resection differed between the two groups due to the different surgical strategies employed based on the location of the tumor. The pathological findings demonstrated that the T stage and AJCC TNM stage were higher in patients with GBC. R0 resection was achieved in 39 (88.6%) patients in the gallbladder group and 11 (84.6%) patients in the bile duct group, but the difference was not significant.

Operative outcomes

The operative data are shown in Table 2. The median operative time was shorter and blood loss was less in the gallbladder group than in the bile duct group; the difference in blood loss was significant between the two groups. Eighteen (40.9%) patients in the gallbladder group and seven (53.8%) patients in the bile duct group received a blood transfusion, and no significant difference was observed. The complication rates were relatively high and similar in both groups. The most common complication was pleural effusion. POPF and bile leakage were two other major complications after HPD in both groups. Posthepatectomy liver failure (≥grade B) was observed in two (4.5%) patients in the gallbladder group and two (15.4%) patients in the bile duct group, but the difference was also nonsignificant.

To determine the safety of major hepatectomy (>3 Couinaud segments) combined with PD, the surgical results were analyzed based on the types of hepatectomy [Table 3]. The amount of blood loss ($P < 0.05$) and operation time ($P < 0.01$) in the major hepatectomy group were greater than those in the minor hepatectomy group. Regarding the short-term outcomes, patients in the major hepatectomy group were more vulnerable to posthepatectomy liver failure ($P = 0.002$) than patients in the minor hepatectomy group.

One postoperative death occurred in the present study: a 48–year–old female patient who underwent left hepatectomy combined with caudate lobectomy and PD. Postoper-

Table 1: Clinicopathological characteristics of 57 patients according to tumor location.

Variable	GBC ($n = 44$)	Cholangiocarcinoma ($n = 13$)	*P* value
Sex (male/female)	15/29	6/7	0.430
Age (years)	58 (40–73)	64 (46–73)	0.227
BMI (kg/m^2)	22.2 (17.3–27.9)	22.7 (18.4–27.1)	0.887
Preoperative tumor markers			
CA19-9 (U/mL)	240.4 (14.23–2038.4)	427.3 (62.8–2094.4)	0.117
CEA (ng/mL)	4.6 (1.6–42.4)	5.2 (2.1–22.7)	0.543
Preoperative biliary drainage	5 (11.4)	6 (46.2)	0.120
PVE	3 (6.8)	2 (15.4)	0.340
Type of hepatic resection			0.001
Limited resection of the gallbladder bed	12 (27.3)	0	
Segments IVa, V	27 (61.4)	0	
Segments I, II, III, IV	0	5 (38.4)	
Segments I, V, VI, VII, VIII	0	8 (61.6)	
Segments I, IV, V, VI, VII, VIII	5 (11.4)	0	
Portal vein resection and reconstruction	4 (9.1)	1 (7.7)	0.880
Adjacent organ resection other than PD	8 (18.2)	0	0.097
Tumor differentiation			0.680
Well and moderate	33 (75)	9 (69.2)	
Poor and undifferentiated	11 (25)	4 (30.8)	
Tumor invasion			0.003
T1	0	2 (15.4)	
T2	10 (22.7)	7 (53.8)	
T3	16 (36.4)	3 (23.1)	
T4	18 (40.9)	1 (7.7)	
Lymph node metastasis			0.223
N0	8 (18.2)	4 (30.8)	
N1	14 (31.8)	6 (46.2)	
N2	22 (50)	3 (23.1)	
TNM stage			0.004
I	0	1 (7.7)	
II	0	1 (7.7)	
III	13 (29.5)	8 (61.6)	
IV	31 (70.5)	3 (23.1)	
R0 resection rate	39 (88.6)	11 (84.6)	0.698
Postoperative chemotherapy	30 (68.2)	4 (30.8)	0.015

Data were presented as *n* (%) or median (interquartile range). BMI: Body mass index; CA 19–9: Carbohydrate antigen 19–9; CEA: Carcinoembryonic antigen; GBC: Gallbladder cancer; PD: Pancreatoduodenectomy; PVE: Portal vein embolization.

Table 2: Operative and perioperative outcomes of patients undergoing HPD according to tumor location.

Variable	GBC ($n = 44$)	Cholangiocarcinoma ($n = 13$)	*P* value
Operative time (min)	350 (280–520)	400 (320–480)	0.092
Blood loss (mL)	600 (200–1500)	800 (400–2300)	0.024
Blood transfusion	18 (40.9)	7 (53.8)	0.409
Complication (≥grade III)	18 (40.9)	6 (46.2)	0.736
Pancreatic fistula (≥grade B)	11 (25)	4 (23.1)	0.678
Bile leakage (≥grade B)	9 (20.5)	2 (15.4)	0.684
Posthepatectomy liver failure (≥grade B)	2 (4.5)	2 (15.4)	0.179
Pleural effusion	15 (34.1)	4 (30.8)	0.823
Intra-abdominal bleeding	3 (6.8)	2 (15.4)	0.377
Sepsis	6 (13.6)	3 (23.1)	0.412
Wound infection	4 (9.1)	1 (7.7)	0.935
Relaparotomy	0	1 (7.7)	0.063
Mortality	0	1 (7.7)	0.063

Data were presented as *n* (%) or median (interquartile range). GBC: Gallbladder cancer; HPD: Hepatopancreatoduodenectomy.

Table 3: Perioperative outcomes of patients undergoing HPD according to types of hepatectomy.

Variable	Major hepatectomy ($n = 18$)	Minor hepatectomy ($n = 39$)	*P* value
Operative time (min)	405 (320–510)	350 (280–520)	0.004
Blood loss (mL)	775 (400–2300)	500 (200–1300)	0.013
Blood transfusion	10 (55.5)	15 (38.5)	0.227
Complication (≥grade III)	8 (44.4)	16 (46.2)	0.808
Pancreatic fistula (≥grade B)	5 (27.8)	10 (25.6)	0.227
Bile leakage (≥grade B)	2 (11.1)	9 (23.1)	0.287
Posthepatectomy liver failure (≥grade B)	4 (22.2)	0	0.002
Pleural effusion	6 (33.3)	13 (33.3)	1.000
Intra-abdominal bleeding	2 (11.1)	3 (15.4)	0.671
Sepsis	4 (22.2)	5 (12.8)	0.366
Wound infection	2 (11.1)	3 (7.7)	0.671
Relaparotomy	1 (5.5)	0	0.138
Mortality	1 (5.5)	0	0.138

Data were presented as *n* (%) or median (interquartile range). HPD: Hepatopancreatoduodenectomy.

ative bile leakage and POPF were detected 1 week after surgery, and the subsequent intra-abdominal bleeding and sepsis were treated with relaparotomy. The patient died 4 days after the second reoperation due to multiple organ failures.

Survival outcomes

After excluding the one postoperative death, the median OS for the 56 patients undergoing HPD was 13 months. OS was longer in patients in the bile duct group {median 31 (95% confidence interval [CI]: 17.1–44.9) months} than in those in the gallbladder group (median 11 [95% CI: 9.4–12.6] months; $P < 0.001$, Figure 2A). Given that the tumor breakthrough serosa and N2 level can significantly affect prognosis, we dichotomized tumor invasion and lymph node metastasis according to tumor breakthrough serosa and N2. In the subgroup analysis of patients in the gallbladder group, T4 stage tumors ($P = 0.002$), N2 tumors ($P = 0.001$), and R1 resection ($P = 0.007$) were significantly associated with poor OS [Table 4]. In the multivariate analysis [Table 4], T4 stage tumors ($P = 0.012$), N2 tumors ($P = 0.001$), and positive margin status ($P = 0.004$) were independently associated with poorer OS. The median survival time (MST) of patients with one or more prognostic factors ($n = 30$) was 9.0 months. In contrast, the MST of patients without these prognostic factors ($n = 14$) was 18.5 months ($P < 0.001$, Figure 2B).

Moreover, a case-control analysis was conducted to determine the influence of HPD on the survival of advanced GBC patients [Table 5]. The overall median survival in the HPD-GBC and None-HPD-GBC groups was 11 months and 12.12 months, respectively ($P > 0.05$, Figure 3).

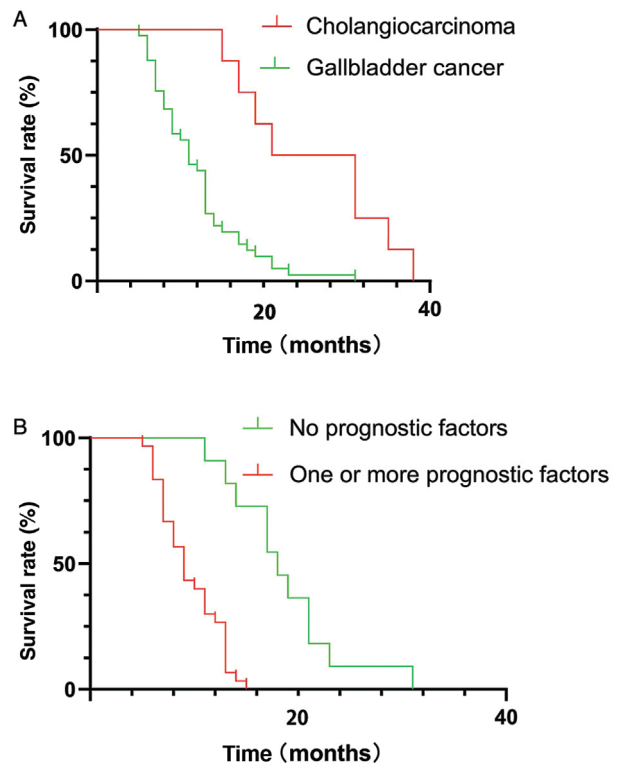

Figure 2: (A) Kaplan–Meier analysis showed a significant difference in OS between the GBC group and the cholangiocarcinoma group ($P < 0.001$). (B) Kaplan–Meier analysis showed a significant difference in GBC patients with or without prognostic factors ($P < 0.001$, HR, 95% CI [3.431, 1.853–6.355]). CI: Confidence interval; GBC: Gallbladder cancer; OS: Overall survival.

Discussion

Complete tumor resection is still the only option to possibly achieve long-term survival. Thus, HPD was performed >20 years ago to achieve curative resection in some patients with locally advanced biliary cancer (ie, biliary cancer with widespread bile duct infiltration and lymph node involvement). HPD is complicated and technically challenging, and the high morbidity and mortality rates in different reports[3-7] have discouraged surgeons from performing this procedure, especially when major hepatectomy is required. In recent years, the mortality rates of HPD have gradually decreased from 0% to 9% according to different studies.[2,16,17] Most recently, Endo *et al*[18] assessed the mortality and morbidity of HPD using a nationwide clinical registry

Table 4: Univariable and multivariable analyses of survival in patients with advanced GBC undergoing HPD.

Variable	Univariable *P* value	Multivariable	
		P value	HR (95%, CI)
Sex (male/female)	0.408	NA	NA
Age >58 years	0.819	NA	NA
BMI >22.2 kg/m^2	0.348	NA	NA
Preoperative biliary drainage	0.906	NA	NA
PVE	0.417	NA	NA
CA19–9 >250 (U/mL)	0.176	NA	NA
CEA >5 (ng/mL)	0.812	NA	NA
Tumor differentiation	0.519	NA	NA
Type of hepatic resection	0.073	NA	NA
PVR	0.947	NA	NA
Adjacent organ resection other than PD	0.126	NA	NA
T4 tumors	0.002	0.012	1.349 (1.068–1.704)
N2 tumors	0.001	0.001	2.861 (1.809–4.525)
R1 resection	0.007	0.004	4.972 (1.693–14.603)
Postoperative chemotherapy	0.475	NA	NA

BMI: Body mass index; CA 19–9: Carbohydrate antigen 19–9; CEA: Carcinoembryonic antigen; CI: Confidence interval; GBC: Gallbladder cancer; HPD: Hepatopancreatoduodenectomy; HR: Hazard ratio; NA: Not applicable; PVR: Portal vein resection; PD: Pancreatoduodenectomy; PVE: Portal vein embolization.

Table 5: Baseline demographics and clinicopathological characteristics in case-match analysis.

Variable	HPD-GBC (*n* = 44)	None-HPD-GBC (*n* = 44)	*P* value
Sex (male/female)	15/29	17/27	0.106
Age (years)	58.0 (40.0–73.0)	57.2 (40.0–72.0)	0.971
BMI (kg/m^2)	22.2 (17.3–27.9)	22.46 (16.1–30.3)	0.823
Preoperative tumor markers			
CA19–9 (U/mL)	240.4 (14.2–2038.4)	487.1 (24.6.8–2401.4)	0.609
CEA (ng/mL)	4.6 (1.6–42.4)	5.29 (2.3–43.7)	0.560
Preoperative biliary drainage	5 (11.4)	8 (18.2)	0.560
PVE	3 (6.8)	5 (11.4)	0.711
Tumor differentiation			0.223
Well and moderate	33 (75.0)	35 (79.5)	
Poor and undifferentiated	11 (25.0)	9 (20.5)	
Tumor invasion			0.682
T1	0	0	
T2	10 (22.7)	11 (25.0)	
T3	16 (36.4)	17 (38.6)	
T4	18 (40.9)	16 (36.4)	
Lymph node metastasis			0.107
N0	8 (18.2)	6 (13.6)	
N1	14 (31.8)	18 (40.9)	
N2	22 (50.0)	20 (45.5)	
R0 resection rate	39 (88.6)	37 (84.1)	0.698
Postoperative chemotherapy	30 (68.2)	33 (75.0)	0.478

Data were presented as *n* (%) or median (interquartile range). BMI: Body mass index; HPD-GBC: Hepatopancreatoduodenectomy gallbladder cancers; PVE: Portal vein embolization.

in Japan. The results indicated that operative mortality decreased significantly in Certified-A institutions, which are required to perform at least 50 major HBP surgeries a year, and they suggested that HPD should be further centralized to reduce operative mortality. In this study, we retrospectively analyzed the operative results of HPD for locally advanced biliary malignancies. There was one in-hospital mortality after HPD, although the morbidity rate was relatively high in both groups. Our results demonstrated that HPD could be performed with a low mortality rate and an acceptable morbidity rate in an experienced high-volume center.

POPF is a major complication after HPD, and fistulas may subsequently trigger other infectious complications and intra-abdominal bleeding.[19-21] Most patients with GBC and cholangiocarcinoma have a soft pancreatic texture and thin pancreatic ducts, which are risk factors for

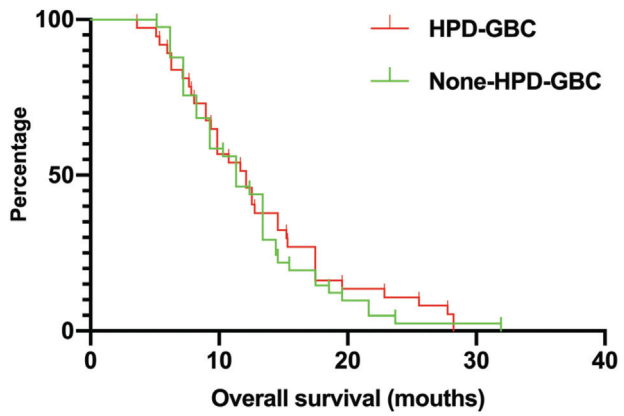

Figure 3: Kaplan–Meier analysis showed the overall median survival in the HPD-GBC and None-HPD-GBC groups was 11 months and 12.12 months, respectively ($P > 0.05$).

POPF.[22,23] Fifteen patients (26.3%) developed POPF (≥grade B) in the present study, and no significant difference was observed between different groups according to the tumor location or type of hepatectomy. Liver failure is another major concern surrounding HPD. In the present study, we noticed that posthepatectomy liver failure occurred only in patients undergoing major hepatectomy combined with PD. Fortunately, none of the patients died due to this complication.

Curative resection was achieved in 84.6% of patients in the bile duct group and 88.6% of patients in the gallbladder group. Patients with cholangiocarcinoma showed a better prognosis than patients with GBC. In addition to the different tumor biology of these two malignancies, the prevalence of TNM stage IV was higher in the gallbladder group than in the bile duct group, which might be another factor contributing to the diverse survival results. The analysis of whether adjuvant chemotherapy affects the prognosis of patients with GBC showed that the prognosis of patients in the adjuvant chemotherapy group was not significantly improved, which may be related to the extreme malignancy of GBC. For patients with advanced GBC, N2 tumors and positive margin status were identified as independent factors of the poorer OS. Patients with none of these factors have better survival, with an MST of 17 months, which is better than that in a phase III trial of currently available first-line systemic therapy for unresectable biliary malignancy.[24,25] Moreover, in the case-match analysis, the HPD-GBC group had a comparable survival result with the None-HPD-GBC group, which indicated that for patients with advanced GBC involved with pancreas or duodenum, HPD might improve the prognosis. Therefore, a careful preoperative assessment may help to identify patients with locally advanced GBC who can possibly achieve R0 resection with HPD when no aggressive lymph node metastasis is detected.

One limitation of this study is the retrospective nature of this small case series. The prognosis of advanced bile duct patients who were potential candidates for HPD but underwent alternative nonsurgical treatment was not available. A randomized controlled trial in one institution is not theoretically possible because of the small number of potential candidates for HPD. Therefore, further prospective multi-institutional studies are needed to objectively elucidate the significance of this complicated operation.

To conclude, HPD could be performed with a low mortality rate and an acceptable morbidity rate in an experienced high-volume center. For patients with advanced GBC without an N2 or T4 tumor, HPD could be a preferable treatment option. Accurate preoperative assessments of the extent of tumor spread with the aim of R0 resection would contribute to improved patient outcomes.

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Conflicts of interest

None.

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