Original Article

Short- and long-term outcomes of laparoscopic versus open resection of perihilar cholangiocarcinoma: a propensity score-based analysis

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Background: Laparoscopic resection (LR) of perihilar cholangiocarcinoma (pCCA) is still in the exploratory stage due to its exacting technical requirements, and its feasibility remains controversial. The objective of this study was to compare the short- and long-term outcomes of LR and open resection (OR) of pCCA.

Methods: This study analyzed the data of pCCA patients who underwent LR or OR from January 2012 to January 2020 at Southwest Hospital. Inverse probability of treatment weighting (IPTW) and propensity score matching (PSM) were used to balance the baseline characteristics between the LR and OR groups. The short- and long-term outcomes were compared between the LR and OR groups.

Results: Forty-five patients in the LR group and 243 in the OR group were analyzed. After IPTW and PSM, the amount of intraoperative blood loss, incidence of surgical site infections (SSIs), length of stay (LOS), and number of perioperative blood transfusions (PBTs) were significantly lower in the LR group than in the OR group (after IPTW: P<0.001, P=0.009, P=0.01, P<0.001 respectively; after PSM: P<0.001, P=0.003, P=0.03, P=0.04 respectively). Only after IPTW was the 30-day mortality rate significantly lower in the LR group than in the OR group (P=0.005). There was no significant difference in overall survival (OS) or recurrence-free survival (RFS) between the two groups after IPTW or PSM.

Conclusions: LR of pCCA is an achievable procedure whose long-term outcomes are similar to those of OR, and LR outperforms OR in short-term outcomes such as intraoperative blood loss, SSI, LOS, 30-day mortality, and PBTs. It is believed that it is safe and feasible to treat pCCA with LR after rigorous patient selection.

Keywords: Perihilar cholangiocarcinoma (pCCA); laparoscopic resection (LR); open resection (OR); inverse probability of treatment weighting (IPTW); propensity score matching (PSM)

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Introduction

Perihilar cholangiocarcinoma (pCCA) is the most common biliary tract tumor, accounting for approximately 50–60% of cases (1). The majority of patients are diagnosed when their tumors are already in the advanced stage. Surgical resection is currently the most effective treatment and the first-line therapeutic option (2).

Due to the location of the pCCA near the porta hepatis, curative-intent resection of the pCCA requires elaborate perihilar skeletonization, vascular resection and reconstruction, hepatectomy, caudate lobectomy, cholangiojejunostomy, etc. (3). Therefore, pCCA resection is considered the most challenging surgery for the hepatobiliary system (4). Surgeons usually select open resection (OR) as the preferred surgical approach (5). This procedure allows more operating space and a wider visual field than laparoscopic resection (LR), thus facilitating complete resection. Nevertheless, with the development of laparoscopic technology, laparoscopic surgery, including laparoscopic hepatectomy and laparoscopic pancreaticoduodenectomy, has been increasingly applied (6,7). These techniques provide a solid foundation for the LR of pCCA. Previous studies have shown that laparoscopic hepatectomy can reduce intraoperative blood loss and morbidity rates and shorten the length of stay (LOS) (8-10). In addition to hepatectomy, key steps of pCCA resection, such as extrahepatic bile duct resection and biliary reconstruction, can also be performed laparoscopically; thus, LR has the opportunity to be performed in selected groups of pCCA patients. At present, several retrospective studies have analyzed the application of LR for pCCA (11-13). However, the number of patients in these studies was small, usually no more than 20, and from a statistical perspective, only propensity score matching (PSM) was applied to control for confounding factors, which further reduced the number of patients.

Inverse probability of treatment weighting (IPTW) creates pseudo-populations through matching scores to control for confounding factors and correct bias caused by small samples (14). To control for confounding factors comprehensively, the present study used both IPTW and PSM to balance the baseline characteristics between LR and OR patients. Intraoperative, postoperative, and long-term outcomes were then compared between the two groups to provide more solid evidence for the safety, feasibility, and efficacy of OR for pCCA. We present this article in accordance with the STROBE reporting checklist (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-23-680/rc).

Highlight box

Key findings

- Laparoscopic resection (LR) of perihilar cholangiocarcinoma (pCCA) did not reduce long-term survival in patients and has advantages in terms of perioperative outcomes.

What is known, and what is new?

- LR of pCCA is a highly challenging procedure, and only a few hepatobiliary centers are able to perform it.
- Laparoscopic surgery for the resection of hilar cholangiocarcinoma has been proven to be a safe and feasible procedure. This approach not only utilizes the perioperative advantages of laparoscopic surgery but also achieves oncological benefits for patients.

What is the implication, and what should change now?

- Most surgeons have typically chosen an open surgical approach for resection of pCCA. However, the results of this study indicate that LR of pCCA can be safely performed in high-volume hepatobiliary centers and can ensure the oncological benefits of surgery.

Methods

Patient selection

This was an observational study. Consecutive pCCA patients who underwent curative-intent resection at the First Affiliated Hospital of Army Medical University (Southwest Hospital) between January 2012 and January 2020 were included. pCCA was defined as a tumor originating between the hepatic duct above the opening of the gallbladder duct and the initiation of the left or right secondary hepatic ducts and was confirmed by postoperative pathological examination. Patients who met any of the following criteria were excluded: (I) had recurrent pCCA, (II) were lost to follow-up, (III) only underwent exploration, or (IV) had missing important variables. This study complied with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committees of Southwest Hospital (ID: KY2021129). Written informed consent of each patient was obtained before surgery and for clinical research.

Surgical procedure

In patients with severe hyperbilirubinemia [total bilirubin (TB) >10 mg/dL] prior to surgery, percutaneous transhepatic cholangial drainage (PTCD) was employed for biliary decompression. For those with moderate but not severe jaundice (TB >3 mg/dL), the determination to proceed with PTCD was based on the patient's overall condition and hepatic function. At our center, patients were requested to filter the drained bile repeatedly and ingest it orally to make it pass through the digestive tract. Current curative-intent resection methods include hepatectomy, extrahepatic bile duct resection, cholangiojejunostomy, and lymph node (LN) dissection. The extent of hepatectomy included the following conditions: (I) right hemihepatectomy; (II) left hemihepatectomy; (III) extended right hemihepatectomy (right hemihepatectomy + partial segment IV resection); (IV) extended left hemihepatectomy (left hemihepatectomy + partial segment V and VIII resection); (V) mesohepatectomy (segment IV, V, and VIII resection); and (VI) dumbbell-form resection (segment IVB and partial segment V resection). All hepatectomies involved caudate lobectomy. Regarding the extent of hepatectomy, as mentioned above, left/right hemihepatectomy was defined by H234/H5678 according to the "New World Terminology" (15), and mesohepatectomy was defined according to a previous surgical perspective (16). Dumbbell-form resection was defined according to a previous surgical perspective at our institution (17). In addition, portal vein resection and reconstruction were performed when the tumor invaded the portal vein (Vp3 or Vp4).

The surgical approaches included LR and OR. The surgical procedure was fundamentally the same for these two approaches. The detailed surgical procedure for LR is shown in Appendix 1. All patients received uniform standardized postoperative care. This study used the incidence of major morbidities to reflect the learning curve of the LR and the OR. In both the LR group and the OR group, the incidence of major morbidities remained stable over time, indicating that the surgical learning curve reached a plateau, as shown in Figure S12.

Data collection

Information on demographics, preoperative liver function and tumor biomarkers, surgery, postoperative pathological examination results, and adjuvant therapy was collected. Specifically, age, sex, medical insurance status, body mass index (BMI), American Society of Anesthesiologists (ASA) score, preoperative jaundice status, PTCD status, cirrhosis status, comorbidity status, adjuvant chemotherapy status, alanine aminotransferase (ALT) status, international normalized ratio (INR), albumin (ALB), carbohydrate antigen 19-9 (CA19-9) status, extent of hepatectomy, Pringle maneuver, tumor size, LN involvement status, macrovascular invasion status, tumor differentiation status, 8th American Joint Committee on Cancer (AJCC) stage, and Bismuth classification were collected.

To facilitate matching, this study converted all continuous variables from baseline characteristics into categorical variables. Specifically, preoperative liver function and tumor biomarkers were divided according to the upper/lower limits of the normal range or cutoff values from previous studies (18-20), such as 40 U/L for ALT, 1.15 for INR, 35 g/L for ALB, and 37 U/L for CA19-9. The World Health Organization considers a BMI ≥25.0 kg/m^2 to indicate overweight, and this value is used to group patients (21). Patients with a tumor size >3 cm seem to have a worse prognosis and are grouped accordingly (18). Based on previous studies, 60 years old was commonly used as the age group for pCCA patients, and patients were therefore grouped accordingly (19,22,23).

Short- and long-term outcomes

Intraoperative outcomes included intraoperative blood loss and operation time. Postoperative outcomes included major morbidity (Clavien-Dindo III/IV) (24), postoperative grade B/C liver failure (as defined by the International Study Group of Liver Surgery) (25), surgical site infection (SSI) (26), pulmonary infection (26), bile leakage (27), intraabdominal sepsis (28), intraabdominal bleeding (29), 30-day morbidity, LOS, perioperative blood transfusion (PBT) (19), and positive surgical margins. Positive surgical margins were defined as those for which the distance between the surgical margin and the tumor was <1 mm. The economic burden included the total cost. Long-term outcomes included overall survival (OS) and recurrence-free survival (RFS). OS was defined as the interval between surgery and death or the last follow-up. RFS was defined as the interval between surgery and recurrence or the last follow-up. Follow-up was performed at Southwest Hospital on a standardized schedule, that is, every 3 months for 2 years after surgery, every 4 months for 3 to 5 years after surgery, and every 6 months for 5 years after surgery, as previously reported (22,30). At each follow-up, abdominal ultrasound examination was performed, and tumor biomarkers and liver function were examined. When tumor recurrence is suspected during abdominal ultrasound examination, doctors strongly recommend that patients undergo computed tomography or magnetic resonance imaging. If

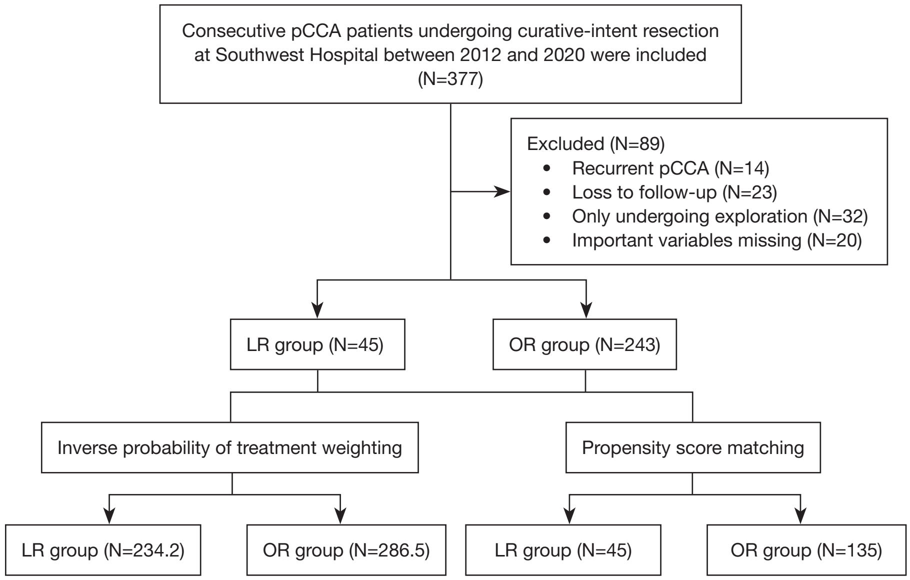

Figure 1 Flow chart of patient selection. pCCA, perihilar cholangiocarcinoma; LR, laparoscopic resection; OR, open resection.

recurrence was confirmed by clinical evaluation, the patient underwent resection again, adjuvant therapy, observation or endoscopic retrograde biliary stent placement. The last follow-up date was June 2022.

Statistical analysis

All patients were divided into an LR group and an OR group according to the resection approach. Both IPTW and PSM based on the propensity score were used to balance the potential confounding variables between the LR and OR groups. This study used a logistic regression model based on all baseline characteristics to estimate propensity scores. In addition, for PSM, one-to-three matching between the two groups was then performed using the nearest-neighbor matching method with a caliper width equal to 0.2 of the standard deviation of the logit of the propensity score. To assess the balancing effect of the baseline characteristics between the two groups, this study calculated the standardized mean difference (SMD) before and after matching (14). An SMD of <0.20 denoted a negligible difference between the two groups (31). The unmatched cohort was defined as the original cohort, and the matched cohort was defined as the cohort after a matching procedure.

Categorical variables are expressed as n (%), and comparisons were conducted by the chi-square test. Continuous variables are expressed as the mean ± standard deviation or median (quartile), and comparisons were conducted by Student's *t* test or the Mann-Whitney U test. K-M curves and log-rank tests were used to estimate and compare the OS and RFS rates. R software version 4.0.2. (https://www.r-project.org/) was used for all the statistical analyses. A P value (two-sided) <0.05 was considered to indicate statistical significance.

Results

Baseline characteristics of the original cohort

In total, 377 pCCA patients treated with curative-intent resection were initially selected for this study; among them, we excluded 14 patients with recurrent pCCA, 23 patients who were lost to follow-up, 32 patients who were only undergoing exploration, and 20 patients whose important variables were missing. Ultimately, a total of 288 pCCA patients were included in the analysis, with 45 patients in the LR group and 243 patients in the OR group, as shown in *Figure 1*. Three patients (6.7%) in the LR group underwent conversion to laparotomy, but they were included in the LR group for analysis. Compared with the OR group, the LR group had a significantly greater proportion of patients who underwent preoperative PTCD (60.0% *vs.* 34.6%, P=0.002) and adjuvant chemotherapy (22.2% *vs.* 10.3%, P=0.045), a nearly significantly greater proportion of patients who underwent the Pringle maneuver (31.1% *vs.* 18.9%, P=0.10) and an earlier 8th AJCC stage (P=0.059). The baseline characteristics before matching between the LR and OR groups are shown in *Table 1*.

Baseline characteristics of the matched cohort

After IPTW, the pseudo-populations of 234.2 patients in the LR group and 286.5 patients in the OR group were analyzed, and after PSM, 45 patients in the LR group and 135 patients in the OR group were analyzed. In the matched cohort, the baseline characteristics of the LR and OR groups were not significantly different, as presented in *Table 2*. The balance of the baseline variables was evaluated using the SMD, which showed that the extent of hepatectomy was the most imbalanced variable, followed by vascular reconstruction and the Bismuth classification after IPTW. After PSM, preoperative PTCD was the most imbalanced variable, followed by the 8th edition AJCC stage and adjuvant therapy, as shown in *Figure 2*. Despite this, the imbalance in all baseline variables between the LR and OR groups was still significantly decreased in the matched cohorts.

Outcomes of the original cohort

Compared with the OR group, the LR group showed significant reductions in the intraoperative blood loss volume (median: 350 *vs.* 600 mL, P<0.001), incidence of SSIs (11.1% *vs.* 32.9%, P=0.006), LOS (median: 19 *vs.* 21 days, P=0.03), and number of PBTs (28.9% *vs.* 48.1%, P=0.03), as well as a nearly significant increase in the operation time (median: 582 *vs.* 526 min, P=0.08). In the LR group, the median follow-up time was 23.2 months, the median OS was 30.4 months, the 5-year OS rate was 30.6%, the median RFS was 23.0 months, and the 5-year RFS rate was 20.7%. In the OR group, the median follow-up time was 25.9 months, the median OS was 29.0 months, the 5-year OS rate was 26.4%, the median RFS was 19.0 months, and the 5-year RFS rate was 20.1%. There was no significant difference in survival rate between the LR and OR groups (P=0.42, P=0.45), as shown in *Figure 3A,3B*. All the outcomes in the original cohort are compared between the LR and OR groups in *Table 3*.

Outcomes in the matched cohorts

After IPTW, compared with the OR group, the LR group showed significant reductions in the intraoperative blood loss volume (median: 200.00 *vs.* 600.0 mL, P<0.001), incidence of SSIs (10.0% *vs.* 34.0%, P=0.009), 30-day mortality (0.0% *vs.* 4.8%, P=0.005), LOS (median: 17.0 *vs.* 21.0 days, P=0.01) and number of PBTs (16.1% *vs.* 48.1%, P<0.001). In the LR group, the 5-year OS rate was 33.2%, and the 5-year RFS rate was 21.7%. In the OR group, the 5-year OS rate was 26.5%, and the 5-year RFS rate was 20.1%. There was no significant difference in either survival rate between the LR and OR groups (P=0.65, P=0.60), as shown in *Figure 3C,3D*.

After PSM, compared with the OR group, the LR group showed significant reductions in the intraoperative blood loss volume (median: 350.0 *vs.* 600.0 mL, P<0.001), incidence of SSIs (11.1% *vs.* 35.6%, P=0.003), LOS (median: 19.0 *vs.* 21.0 days, P=0.03) and number of PBTs (28.9% *vs.* 46.7%, P=0.04). In the LR group, the 5-year OS rate was 33.2%, and the 5-year RFS rate was 21.7%. In the OR group, the 5-year OS rate was 26.4%, and the 5-year RFS rate was 18.8%. There was no significant difference in either survival rate between the LR and OR groups (P=0.45, P=0.37), as shown in *Figure 3E,3F*.

All the outcomes in the matched cohorts are compared between the LR and OR groups in *Table 4*.

Discussion

With the rapid development of laparoscopic techniques and instruments, much experience has accumulated in complex surgeries such as laparoscopic hepatectomy, laparoscopic cholangiojejunostomy, and laparoscopic regional LN dissection (32,33). These surgical techniques are also key procedures necessary for curative-intent resection of pCCA, laying a foundation for further development and exploration of LR of pCCA.

In recent years, many researchers have compared the efficacy and safety of LR with those of OR in the treatment of pCCA. Zhang *et al.* collected the data of 25 pCCA patients, including 14 patients in the LR group and 9 patients in the OR group, and found that LR required a significantly longer operation, but there was no significant difference in OS or other postoperative outcomes (12). He *et al.* collected data from 83 pCCA patients. After PSM, 16 patients in the LR group and 32 patients in the OR group were included for analysis; the analysis showed that there were no significant differences in postoperative outcomes between the LR and OR groups, but the operation duration was significantly longer in the LR group (11). Ma *et al.* collected data from 149 pCCA patients after PSM,

Table 1 Comparison of baseline characteristics of the original cohort between the LR and OR groups in perihilar cholangiocarcinoma

Variables	LR group (N=45)	OR group (N=243)	P value
Age >60 years	23 (51.1)	106 (43.6)	0.44
Male	24 (53.3)	143 (58.8)	0.60
Medical insurance	31 (68.9)	192 (79.0)	0.19
BMI ≥25.0 kg/m^2	5 (11.1)	32 (13.2)	0.89
ASA score > grade II	1 (2.2)	14 (5.8)	0.54
Preoperative jaundice	34 (75.6)	203 (83.5)	0.28
Preoperative PTCD	27 (60.0)	84 (34.6)	0.002
Cirrhosis	4 (8.9)	21 (8.6)	>0.99
Comorbidity	6 (13.3)	45 (18.5)	0.53
Adjuvant chemotherapy	10 (22.2)	25 (10.3)	0.045
ALT >40 U/L	40 (88.9)	205 (84.4)	0.58
INR >1.15	1 (2.2)	11 (4.5)	0.76
ALB <35 g/L	12 (26.7)	83 (34.2)	0.42
CA19-9 >37 U/L	42 (93.3)	225 (92.6)	>0.99
Extent of hepatectomy			0.56
Right hemihepatectomy	2 (4.4)	5 (2.1)	
Extended right hemihepatectomy	10 (22.2)	37 (15.2)	
Left hemihepatectomy	1 (2.2)	13 (5.3)	
Extended left hemihepatectomy	20 (44.4)	111 (45.7)	
Mesohepatectomy	8 (17.8)	40 (16.5)	
Dumbbell-form resection	4 (8.9)	37 (15.2)	
PV resection and reconstruction	5 (11.1)	46 (18.9)	0.29
Pringle maneuver	14 (31.1)	46 (18.9)	0.10
Tumor size >3 cm	17 (37.8)	76 (31.3)	0.49
LN involvement	20 (44.4)	106 (43.6)	>0.99
Macrovascular invasion	13 (28.9)	86 (35.4)	0.50
Tumor poor differentiation	11 (24.4)	40 (16.5)	0.28
8th AJCC stage			0.059
Stage I	6 (13.3)	38 (15.6)	
Stage II	18 (40.0)	52 (21.4)	
Stage III	18 (40.0)	137 (56.4)	
Stage IV	3 (6.7)	16 (6.6)	
Bismuth classification			0.39
Class I	4 (8.9)	43 (17.7)	
Class II	8 (17.8)	34 (17.7)	
Class III	29 (64.4)	136 (56.0)	
Class IV	4 (8.9)	30 (12.3)	

Data are presented as n (%). LR, laparoscopic resection; OR, open resection; BMI, body mass index; ASA, American Society of Anesthesiologists; PTCD, percutaneous transhepatic cholangial drainage; ALT, alanine aminotransferase; INR, international normalized ratio; ALB, albumin; CA19-9, carbohydrate antigen 19-9; LN, lymph node; PV, portal vein; AJCC, American Joint Committee on Cancer.

Table 2 Comparison of baseline characteristics of the matched cohorts between the LR and OR groups in perihilar cholangiocarcinoma

Variables	After IPTW			After PSM		
	LR group (N=234.2)	OR group (N=286.5)	P value	LR group (N=45)	OR group (N=135)	P value
Age >60 years	95.9 (40.9)	128.6 (44.9)	0.71	23 (51.1)	65 (48.1)	0.86
Male	109.6 (46.8)	164.9 (57.6)	0.32	24 (3.3)	74 (54.8)	>0.99
Medical insurance	173.1 (73.9)	223.2 (77.9)	0.63	31 (68.9)	100 (74.1)	0.63
BMI ≥25.0 kg/m^2	33.9 (14.5)	36.6 (12.8)	0.83	5 (11.1)	19 (14.1)	0.80
ASA score > II grade	11.4 (4.9)	15.0 (5.2)	0.94	1 (2.2)	7 (5.2)	0.68
Preoperative jaundice	175.8 (75.1)	233.8 (81.6)	0.47	34 (75.6)	106 (78.5)	0.84
Preoperative PTCD	94.0 (40.1)	107.9 (37.7)	0.80	27 (60.0)	65 (48.1)	0.23
Cirrhosis	11.9 (5.1)	24.2 (8.4)	0.37	4 (8.9)	14 (10.4)	>0.99
Comorbidity	51.0 (21.8)	50.5 (17.6)	0.68	6 (13.3)	25 (18.5)	0.29
Adjuvant chemotherapy	39.6 (16.9)	35.3 (12.3)	0.56	10 (22.2)	19 (14.1)	0.29
ALT >40 U/L	200.4 (85.6)	243.5 (85.0)	0.95	40 (88.9)	116 (85.9)	0.80
INR >1.15	3.6 (1.5)	11.8 (4.1)	0.33	1 (2.2)	4 (3.0)	>0.99
ALB <35 g/L	58.0 (24.8)	93.5 (32.6)	0.40	12 (26.7)	46 (34.1)	0.46
CA19-9 >37 U/L	224.6 (95.9)	265.6 (92.7)	0.38	42 (93.3)	128 (94.8)	>0.99
Extent of hepatectomy			0.70			0.99
Right hemihepatectomy	5.1 (2.2)	9.0 (3.1)		2 (4.4)	5 (3.7)	
Extended right hemihepatectomy	63.5 (27.1)	46.2 (16.1)		10 (22.2)	27 (20.0)	
Left hemihepatectomy	20.0 (8.5)	14.3 (5.0)		1 (2.2)	5 (3.7)	
Extended left hemihepatectomy	94.8 (40.5)	130.4 (45.5)		20 (44.4)	58 (43.0)	
Mesohepatectomy	21.6 (9.2)	46.1 (16.1)		8 (17.8)	24 (17.8)	
Dumbbell-form resection	29.3 (12.5)	40.5 (14.1)		4 (8.9)	16 (11.9)	
PV resection and reconstruction	17.9 (7.6)	51.1 (17.8)	0.07	5 (11.1)	15 (11.1)	>0.99
Pringle maneuver	44.9 (19.2)	57.8 (20.2)	0.90	14 (31.1)	33 (24.4)	0.49
Tumor size >3 cm	41.8 (17.8)	74.5 (26.0)	0.41	9 (20.0)	29 (21.5)	>0.99
LN involvement	94.2 (40.2)	124.7 (43.5)	0.76	20 (44.4)	61 (45.2)	>0.99
Macrovascular invasion	58.3 (24.9)	99.3 (34.7)	0.30	13 (28.9)	39 (28.9)	>0.99
Tumor poor differentiation	23.7 (10.1)	47.4 (16.5)	0.19	11 (24.4)	24 (17.8)	0.45
8th AJCC stage			0.80			0.55
Stage I	54.4 (23.2)	46.3 (16.2)		6 (13.3)	23 (17.0)	
Stage II	53.1 (22.7)	65.8 (23.0)		18 (40.0)	39 (28.9)	
Stage III	107.9 (46.1)	155.8 (54.4)		18 (40.0)	65 (48.1)	
Stage IV	18.9 (8.1)	18.6 (6.5)		3 (6.7)	8 (5.9)	

Table 2 *(continued)*

Table 2 *(continued)*

Variables	After IPTW			After PSM		
	LR group (N=234.2)	OR group (N=286.5)	P value	LR group (N=45)	OR group (N=135)	P value
Bismuth classification			0.70			0.96
Class I	29.3 (12.5)	46.5 (16.2)		4 (8.9)	16 (11.9)	
Class II	21.6 (9.2)	40.1 (14.0)		8 (17.8)	24 (17.8)	
Class III	163.9 (70.0)	167.5 (58.5)		29 (64.4)	84 (62.2)	
Class IV	19.5 (8.3)	32.4 (11.3)		4 (8.9)	11 (8.1)	

Data are presented as n (%). LR, laparoscopic resection; OR, open resection; IPTW, inverse probability of treatment weighting; PSM, propensity score matching; BMI, body mass index; ASA, American Society of Anesthesiologists; PTCD, percutaneous transhepatic cholangial drainage; ALT, alanine aminotransferase; INR, international normalized ratio; ALB, albumin; CA19-9, carbohydrate antigen 19-9; LN, lymph node; PV, portal vein; AJCC, American Joint Committee on Cancer.

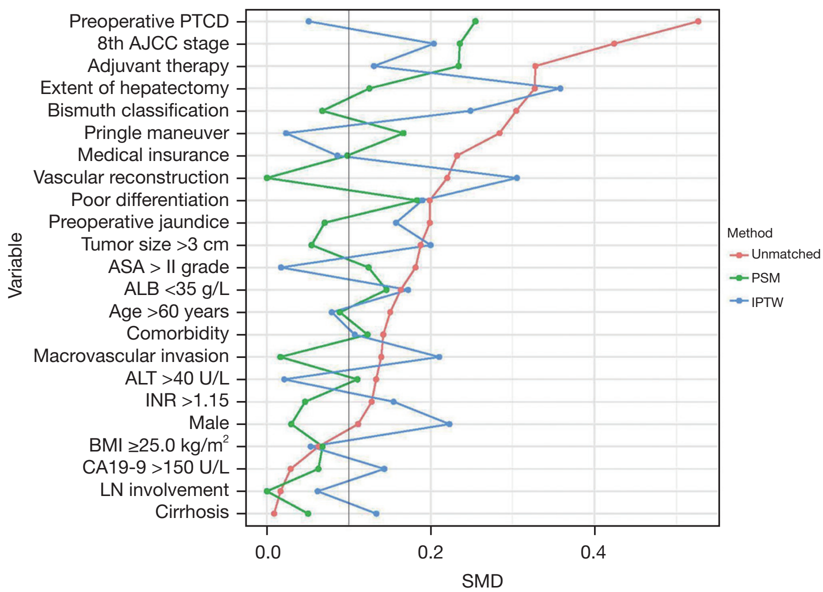

Figure 2 Distribution of the SMD of confounding factors in the original and matched cohorts between the LR and OR groups. SMD, standardized mean difference; BMI, body mass index; ASA, American Society of Anesthesiologists; PTCD, percutaneous transhepatic cholangial drainage; ALT, alanine aminotransferase; INR, international normalized ratio; ALB, albumin; CA19-9, carbohydrate antigen 19-9; LN, lymph node; AJCC, American Joint Committee on Cancer; IPTW, inverse probability of treatment weighting; PSM, propensity score matching; LR, laparoscopic resection; OR, open resection.

including 20 in the LR group and 47 in the OR group, and reported a significantly shorter surgical incision length and poorer OS in the LR group than in the OR group; however, they also explained that the difference in OS might be due to the significantly longer follow-up time in the OR group (13). These previous studies have shown that LR has similar safety and efficacy to OR in the treatment of pCCA.

However, all previous studies have the same shortcomings. Specifically, to adjust for confounding factors between the LR group and OR group, PSM was used to balance the baseline characteristics of the two groups. However, in the course of PSM, there must be a reduction in the overall study cohort. This would affect the comparison of treatment outcomes after matching, especially for a cohort with a small

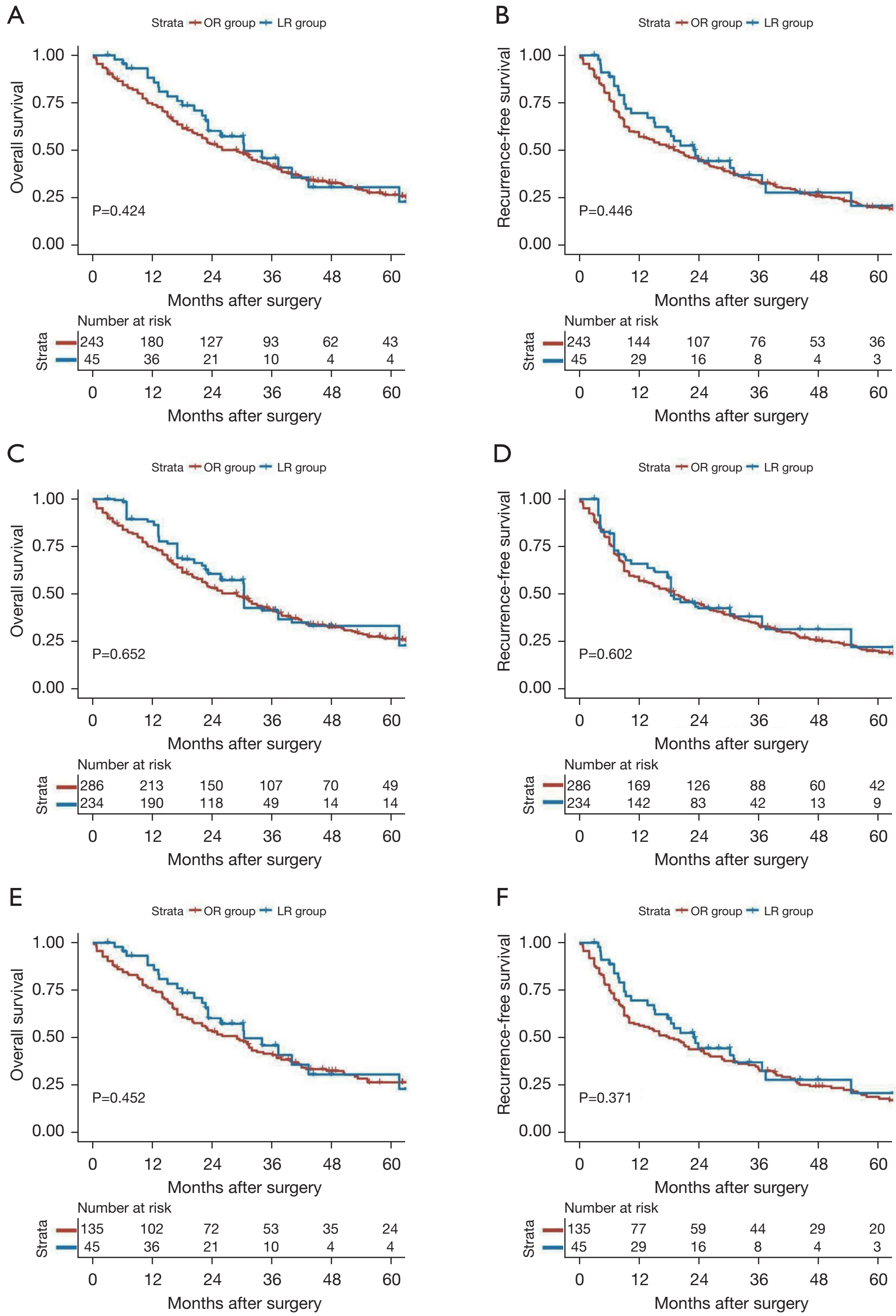

Figure 3 Comparison of survival curves of the LR and OR groups in the original cohort, after IPTW, and after PSM in perihilar cholangiocarcinoma. OS in the original cohort (A). RFS in the original cohort (B). OS after IPTW (C). RFS after IPTW (D). OS after PSM (E). RFS after PSM (F). OS, overall survival; LR, laparoscopic resection; OR, open resection; IPTW, inverse probability of treatment weighting; RFS, recurrence-free survival; PSM, propensity score matching.

Table 3 Comparison of outcomes of the original cohort between the LR and OR groups in perihilar cholangiocarcinoma

Outcomes	LR group (N=45)	OR group (N=243)	P value
Intraoperative outcomes			
Intraoperative blood loss*, mL	350.0 (200.0, 500.0)	600.0 (400.0, 1,000.0)	<0.001
Operation time*, min	582.0 (469.0, 638.0)	526.0 (410.0, 604.0)	0.08
Postoperative outcomes			
Major morbidity	8 (17.8)	49 (20.2)	0.87
Post-operative grade B/C liver failure	2 (4.4)	10 (4.1)	>0.99
Surgical site infection	5 (11.1)	80 (32.9)	0.006
Pulmonary infection	4 (8.9)	40 (16.5)	0.28
Bile leakage	6 (13.3)	34 (14.0)	>0.99
Intraabdominal sepsis	1 (2.2)	6 (2.5)	>0.99
Intraabdominal bleeding	4 (8.9)	27 (11.1)	0.86
30-day mortality	0 (0.0)	11 (4.5)	0.15
Length of stay*, days	19 (16, 23)	21 (17, 28)	0.03
Perioperative blood transfusion	13 (28.9)	117 (48.1)	0.03
Positive surgical margins	4 (8.9)	14 (5.8)	0.65
Economic burden			
Total cost*, RMB	127,749.0 (104,482.0, 158,621.0)	129,475.0 (94,737.0, 178,913.0)	0.70
Long-term outcomes			
Follow-up time*, months	23.2 (13.3, 34.1)	25.9 (11.0, 48.0)	0.46
Death during follow-up	24 (53.3)	183 (75.3)	0.005
Median OS**, months	30.4 (23.2, NA)	29.0 (23.0, 34.3)	0.42
5-year OS, %	30.6	26.4	
Recurrence during follow-up	28 (62.2)	202 (83.1)	0.48
Median RFS**, months	23.0 (15.2, 37.4)	19.0 (14.0, 25.1)	0.45
5-year RFS, %	20.7	20.1	

Data are presented as n (%) unless otherwise stated. *, values are expressed as the median (quartile); **, values are expressed as the median and 95% confidence interval. LR, laparoscopic resection; OR, open resection; OS, overall survival; NA, not available; RFS, recurrence-free survival.

sample size; therefore, this reduction needs to be avoided. IPTW is a matching method to avoid loss of sample size; this method uses two original populations to create two pseudo-populations to balance the differences in covariates between the two primary populations and make the two groups comparable (14).

To our knowledge, this is the first study to use both IPTW and PSM to control for confounding factors and compare the short- and long-term outcomes of LR and OR for pCCA patients who underwent curative-intent resection. The findings of this study are as follows.

The intraoperative blood loss volume, incidence of SSIs, LOS, and number of PBTs were significantly lower in the LR group than in the OR group in both the original and matched cohorts. Laparoscopic techniques have been shown to reduce blood loss and LOS when used during hepatectomy (8-10). In addition, the main cause of PBT is excessive blood loss. If blood loss is reduced, the need

Table 4 Comparison of outcomes of the matched cohorts between LR and OR groups in perihilar cholangiocarcinoma

Outcomes	After IPTW			After PSM		
	LR group (N=234.2)	OR group (N=286.5)	P	LR group (N=45)	OR group (N=135)	P
Intraoperative outcomes						
Intraoperative blood loss*, mL	200.00 (200.00, 397.39)	600.00 (400.00, 976.30)	<0.001	350.00 (200.00, 500.00)	600.00 (400.00, 1000.00)	<0.001
Operation time*, min	503.83 (402.92, 625.00)	526.00 (410.00, 605.19)	0.67	582.00 (469.00, 638.00)	525.00 (429.00, 598.50)	0.14
Postoperative outcomes						
Major morbidity	58.0 (24.8)	60.9 (21.2)	0.73	8 (17.8)	28 (20.7)	0.83
Post-operative grade B/C liver failure	21.8 (9.3)	12.0 (4.2)	0.38	2 (4.4)	5 (3.7)	>0.99
Surgical site infection	23.3 (10.0)	97.4 (34.0)	0.009	5 (11.1)	48 (35.6)	0.003
Pulmonary infection	21.9 (9.3)	50.2 (17.5)	0.37	4 (8.9)	27 (20.0)	0.14
Bile leakage	27.4 (11.7)	40.9 (14.3)	0.74	6 (13.3)	21 (15.6)	0.90
Intraabdominal sepsis	6.5 (2.8)	7.0 (2.4)	0.90	1 (2.2)	6 (4.4)	0.82
Intraabdominal bleeding	19.8 (8.4)	31.1 (10.9)	0.69	4 (8.9)	15 (11.1)	0.89
30-day mortality	0.0 (0.0)	13.8 (4.8)	0.005	0 (0.0)	6 (4.4)	0.34
Length of stay*, days	17.00 (15.65, 22.00)	21.00 (17.00, 28.00)	0.01	19.00 (16.00, 23.00)	21.00 (17.00, 29.00)	0.03
Perioperative blood transfusion	37.8 (16.1)	137.8 (48.1)	<0.001	13 (28.9)	63 (46.7)	0.04
Positive surgical margins	26.3 (11.2)	16.3 (5.7)	0.38	4 (8.9)	9 (6.7)	0.87
Economic burden						
Total cost*, RMB	127,189.20 (99,492.19, 154,991.62)	129,532.10 (94,720.25, 178,913.00)	0.82	127,749.00 (104,482.00, 158,621.00)	131,394.00 (99,099.00, 175,807.50)	0.49
Long-term outcomes						
Follow-up time*, months	23.51 (12.99, 34.08)	25.90 (11.00, 47.45)	0.52	NA	NA	
Death during follow-up	128.8 (55.0)	213.9 (74.7)	0.046	24 (53.3)	103 (76.3)	0.006
Median OS**, months	30.4 (18.0, NA)	29.0 (22.7, 34.3)	0.65	30.4 (23.2, NA)	29.0 (20.3, 37.0)	0.45
5-year OS, %	33.2	26.5		33.2	26.4	
Recurrence during follow-up	143.4 (61.2)	237.3 (82.8)	0.01	28 (62.2)	115 (85.2)	0.002
Median RFS**, months	18.4 (10.4, NA)	19.0 (14.0, 26.0)	0.60	18.4 (10.4, NA)	18.0 (10.0, 26.3)	0.37
5-year RFS, %	21.7	20.1		21.7	18.8	

Data are presented as n (%) unless otherwise stated. *, values are expressed as the median (quartile); **, values are expressed as the median and 95% confidence interval. LR, laparoscopic resection; OR, open resection; IPTW, inverse probability of treatment weighting; PSM, propensity score matching; OS, overall survival; RFS, recurrence-free survival; NA, not available.

for PBT is also reduced as a natural consequence. The incidence of SSIs in the LR group was significantly lower than that in the OR group in the original and matched cohorts. LR uses a shorter incision than does OR and produces a minimal inflammatory response at the surgical site, thereby reducing the risk of SSI (34). The longer the incision is exposed to air, the greater the risk of SSI. The internal and external environments were isolated under pneumoperitoneum maintenance, reducing the incision length and air contact time. In addition, increased blood loss can lead to abnormal tissue healing, increasing the risk of SSI. The volume of blood loss was significantly greater in the OR group than in the LR group in this study, increasing the risk of SSI in OR recipients (35). There was no significant difference in 30-day mortality between the two groups in the original cohort, but after IPTW, the 30-day mortality rate was significantly lower in the LR group than in the OR group. This may be related to bias in patient selection. In preoperative evaluations, surgeons recommend that patients with more difficult surgical requirements and later-stage tumors choose OR over LR, which is a major reason for the 0% 30-day mortality rate in the LR group in this study.

There was no significant difference in the 5-year OS or RFS rate between the two groups in the original cohort or the matched cohort. In general, pneumoperitoneum is believed to affect the immune status of the body and increase abdominal implantation and dissemination of the tumor, thereby reducing OS (36,37). However, the risk that pneumoperitoneum will increase tumor spread in the LR of pCCA patients has not been supported by empirical medical evidence, and the OS and RFS rates in the LR and OR groups were similar in this study. This may be related to the high degree of malignancy of pCCA. Even after R0 resection, the 5-year RFS rate of PCCA patients remains low, at less than 20% (18). The highly malignant nature of the tumor may mask the implantation and dissemination of the tumor caused by pneumoperitoneum. In addition, despite matching, it is important to note that those in the LR group had an earlier tumor stage and a shorter length of follow-up than those in the OR group, which may also be one of the reasons for the lack of a difference in the OS and RFS rates.

Additionally, in the original cohort, the rate of PTCD in the LR group was significantly lower than that in the OR group. The reason for this phenomenon was that because LR is a new technique, prompted surgeons tend to perform more aggressive preoperative preparation, thereby reducing the burden on the liver and reducing surgical risk. However, this difference was effectively balanced between the PSM and IPTW cohorts. Although laparoscopy is an increasingly mature technique and was confirmed in this study to benefit pCCA patients in the short term, there is still much controversy regarding the selection of LR versus OR in pCCA, which can be seen from the differences in the baseline characteristics of the two groups. At present, because laparoscopic pCCA resection is still in the exploratory stage at most HPB institutions, there are no international medical guidelines or consensuses to guide the selection of surgical approaches. In China, there is an expert consensus indicating that LR can be performed for Bismuth class I, II, and some III pCCA patients without macrovascular invasion (38). Before the learning curve of laparoscopic pCCA resection in our center, Bismuth I, II, and some III classification pCCA patients without macrovascular invasion will be informed that they can choose to undergo laparoscopic surgery. However, as laparoscopic technology matures and surgeons gain more experience, our center will also inform Bismuth IV or patients with macrovascular invasion that they can choose to undergo laparoscopic surgery.

Due to the large number of bile duct openings, some of which are very narrow, cholangiojejunostomy is the most difficult step of curative-intent resection for pCCA. Conventional wisdom might suggest that an open approach is better for complex surgical procedures. However, compared with the open approach, laparoscopic surgery can magnify the field of view of the operation area, and the surgeon can see the operation area more directly and clearly. In other words, the laparoscopic approach may be more beneficial for surgeons to perform more delicate operations. In this study, there was no significant difference in the incidence of postoperative bile leakage between the LR and OR groups, suggesting that the incidence of bile leakage is not affected by the use of an open or laparoscopic approach.

The hepatic artery and portal vein are commonly invaded by the pCCA. Resection combined with vascular reconstruction should be performed in patients with macrovascular invasion on the preserved side. However, Matsuyama *et al.* retrospectively analyzed the clinical data of 98 pCCA patients who underwent vascular reconstruction and reported that although combined vascular reconstruction resulted in R0 rates similar to those achieved without vascular invasion, it did not improve the survival rate of patients without vascular reconstruction (39). This observation may be related to the tumor biology of pCCA. Therefore, vascular reconstruction for pCCA patients with macrovascular invasion needs to be carefully evaluated. In addition, laparoscopic revascularization is very difficult. The mainland Chinese guidelines state that OR or conversion to open surgery is recommended for patients with pCCA combined with macrovascular invasion (38). However, in this study, our surgical team performed portal vein reconstruction in patients with macrovascular invasion on the preserved side (5 patients), and the 30-day mortality rate was 0%. We believe that laparoscopic revascularization is safe and feasible when performed by an experienced hepatobiliary surgeon after a long period of surgical training.

In this study, the results from the two matching methods had similarities and differences. Similarly, the intraoperative blood loss volume, incidence of SSIs, LOS, and number of PBTs were lower in the LR group. The difference was that the 30-day mortality rate was lower in the LR group only after IPTW and not after PSM. In our opinion, the results obtained after both IPTW and PSM are more robust. However, this does not mean that the results of significant differences after IPTW alone are meaningless. As we have mentioned before, IPTW avoids sample size losses by creating pseudo-populations; therefore, the results obtained after IPTW alone may correspond to what can be expected after the LR of pCCA is carried out on a large scale. In other words, when the laparoscopic approach is more widely used for curative resection of pCCA, there may be a potential advantage in reducing the incidence of 30-day mortality. Notably, this hypothesis needs further validation in larger cohorts to confirm its potential benefit.

This study has the following limitations: (I) this was a single-center retrospective study. We tried to include other hospitals, but the quality of this surgery varied among different hospitals; thus, the inclusion of other hospitals may have resulted in greater bias in the results. (II) The LR group and the OR group had large differences at baseline. After IPTW and PSM in this study, some SMDs of the baseline characteristics were still greater than 0.1. In fact, these differences are difficult to eliminate, but they approximate real-world circumstances. (III) Only 45 pCCA patients underwent LR. The small number of cases results in a limited level of evidence, but regarding the LR of pCCA, this study already includes the largest number of cases reported thus far. (IV) All extended hemihepatectomies were either H4'5678 or H2345'8'. Therefore, the results of this study may only be applicable to patients undergoing this type of hepatectomy. If hepatectomy involves the H45678 (right trisectionectomy) or H23458 (left trisectionectomy) range, further study validation is needed to confirm the conclusions of this study.

Conclusions

For pCCA patients, LR can reduce blood loss, PBT requirements and SSIs and shorten the LOS, with a total cost similar to that of OS and OR. When LR is implemented on a large scale, it is possible to reduce the 30-day mortality rate. The new surgical technique of LR does not actually change the surgical principle; only the surgical approach and methods have changed. Our research results confirm the obvious advantages of laparoscopic pCCA resection in terms of short-term outcomes, and the long-term outcomes are generally similar to those of open pCCA resection. We believe that it is safe and feasible to treat pCCA with LR after rigorous patient selection. At experienced institutions, suitable pCCA patients should be recommended for laparoscopic surgery.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-23-680/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-23-680/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study complied with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committees of Southwest Hospital (ID: KY2021129). Written informed consent of each patient was obtained before surgery and for clinical research.

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