



Total Hilar En Bloc Resection with Left Hemihepatectomy and Caudate Lobectomy: a Novel Approach for Treatment of Left-Sided Perihilar Cholangiocarcinoma (with Video)

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Abstract

Background “Hilar en bloc resection” using a no-touch technique has been advocated as a standard procedure in right-sided hepatectomies for treatment of perihilar cholangiocarcinoma (PHC). In principle, it has never been reported for left-sided tumors. The aim is to describe the procedures of total hilar en bloc resection with left hemihepatectomy and caudate lobectomy (THER-LH) for advanced PHC and discuss feasibility and clinical significance of this novel technique.

Methods A retrospective study using a prospectively maintained database was performed to identify eight patients who had received THER-LH for advanced PHC from January 2013 to December 2015. The clinicopathological features, surgical procedures, and outcomes of these patients form the basis this study.

Results The operative time was 546 ± 158 (380–870) min, and estimated blood loss was 875 ± 690 (400–2500) ml. Time of vessel resection and reconstruction was 25.6 ± 12.3 min for the portal vein and 19.1 ± 4.9 min for the hepatic artery. Time of hilum clamping was 27.3 ± 11.9 (15–41) min. Two patients had Clavien-Dindo grade II and IVa complications of bile leakage with one developing intraabdominal abscess and bleeding. There was no perioperative mortality. Histopathologic examination revealed that all of eight patients had tubular adenocarcinoma with microscopic invasion to the resected hepatic arteries and portal veins in seven patients. Negative bile duct margins were achieved in all of them. Three patients developed recurrence and died at 11, 18, and 24 months postoperatively. The remaining patients were alive at the time of last follow-up. The median survival was 24 months with one patient achieving a disease-free survival of 50 months.

Synopsis We described our technique of total hilar en bloc resection with left hemihepatectomy and caudate lobectomy for eight patients with advanced PHC and discussed its feasibility. It is a technically demanding procedure that is safe and feasible and may have some beneficial effects on the prognosis of these patients.

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Conclusion THER-LH is a technically demanding procedure that is safe and feasible that may have some beneficial effects on the prognosis of these patients with advanced PHC. Further studies are required to confirm the oncological superiority and survival benefits of this novel technique.

Keywords Perihilar cholangiocarcinoma · Hilar en bloc resection · Left hemihepatectomy

Introduction

Perihilar cholangiocarcinoma (PHC) is the most common malignant tumor affecting extrahepatic bile ducts, and surgical resection represents the only curative option. Given the close proximity of the bile duct bifurcation to vascular inflow, perihilar vasculature invasion is common and historically been the main cause for unresectability.¹ While portal vein (PV) resection has become routine, hepatic artery (HA) involvement remains an obstacle.^{2–9} “Hilar en bloc resection” using a “no-touch technique” with hepatectomy has been recommended for treatment of advanced PHC.^{10–12} The survivals of patients undergoing hilar en bloc resection for right-sided PHC are reported to be significantly higher than those after standard resection.¹¹ However, in principle, hilar en bloc resection has never been reported for left-sided tumors given technical difficulty and fear of associated morbidity and mortality.^{10–14} As the refinement of surgical technique developed in liver transplantation, we have advocated an aggressive surgical strategy to perform major hepatectomy with simultaneous resection of the PV and HA for the treatment of PHC from 2012. Here, we report a novel technique of performing total hilar en bloc resection with left hemihepatectomy and caudate lobectomy (THER-LH) for treatment of left-sided PHC.

Methods

Patients

From January 2005 to December 2015, a total of 128 consecutive patients with PHC underwent surgical exploration with the intention of performing curative resection at the Department of Hepatobiliary and Pancreatic Surgery, Lihuili Hospital of Ningbo University, Ningbo, China. A retrospective study using a prospectively maintained database was performed to identify patients who had received THER-LH. Between January 2013 to December 2015, forty-seven consecutive patients with PHC underwent curative resection, and eight patients had received THER-LH.

Patients diagnosed with PHC were evaluated using computed tomography and magnetic resonance cholangiopancreatography (MRCP) to determine Bismuth-

Corlette classification, vascular invasion, and metastatic disease. Three dimensional visualization technologies were applied to help making surgical procedures individually from 2015 (Video 1). Left hemihepatectomy combined with caudate lobectomy was considered for type IIIb or IV PHC with tumor extension predominantly in the left side. The preliminary decision to perform a THER-LH was made based on preoperative imaging that the tumor abutted or encircled the PV and HA in hilum. When the findings were confirmed by palpation by the surgeons, that the HA and PV at the hilum were involved and could not be freed from tumor, THER-LH was performed, when there were no contraindications. Clinicopathological and follow-up data of the eight patients were collected to form the basis of this retrospective study.

Surgical Procedures

Surgical procedures of THER-LH are described sequentially and illustrated by Figs. 1, 2 and Video 2.

- Step 1. After laparotomy, the whole abdominal cavity is thoroughly examined to confirm the absence of liver metastasis and disseminated disease. The extension of tumor invasion and vascular involvement are confirmed. Kocher’s maneuver is used to facilitate all subsequent procedures and to confirm the absence of para-aortic lymph node metastasis by obtaining frozen sections. Clearance of the para-aortic lymph node is not performed routinely unless microscopic metastasis of these nodes is observed (Figs. 1a, b and 2a).
- Step 2. The dissection of hepatoduodenal ligament (HDL) begins at level of the pancreas and duodenum with transection of the right gastric artery (RGA) followed by dissection along gastroduodenal artery (GDA), which is divided as close to the pancreas as possible. The proper hepatic artery (PHA) and the main portal vein (MPV) are identified and isolated using vessel loops. A complete lymphadenectomy of HDL is performed, including the clearance of para-aortic lymph nodes and soft tissues in the case where metastasis to these nodes has been confirmed, proceeding proximally to the hilum with skeletonization of the PHA and the MPV. The distal common bile duct (CBD) is then divided at its entrance into the pancreas. Frozen sections of the margin of the CBD stump are performed to ensure that a Whipple procedure is not necessary. The dissection toward the hilum is

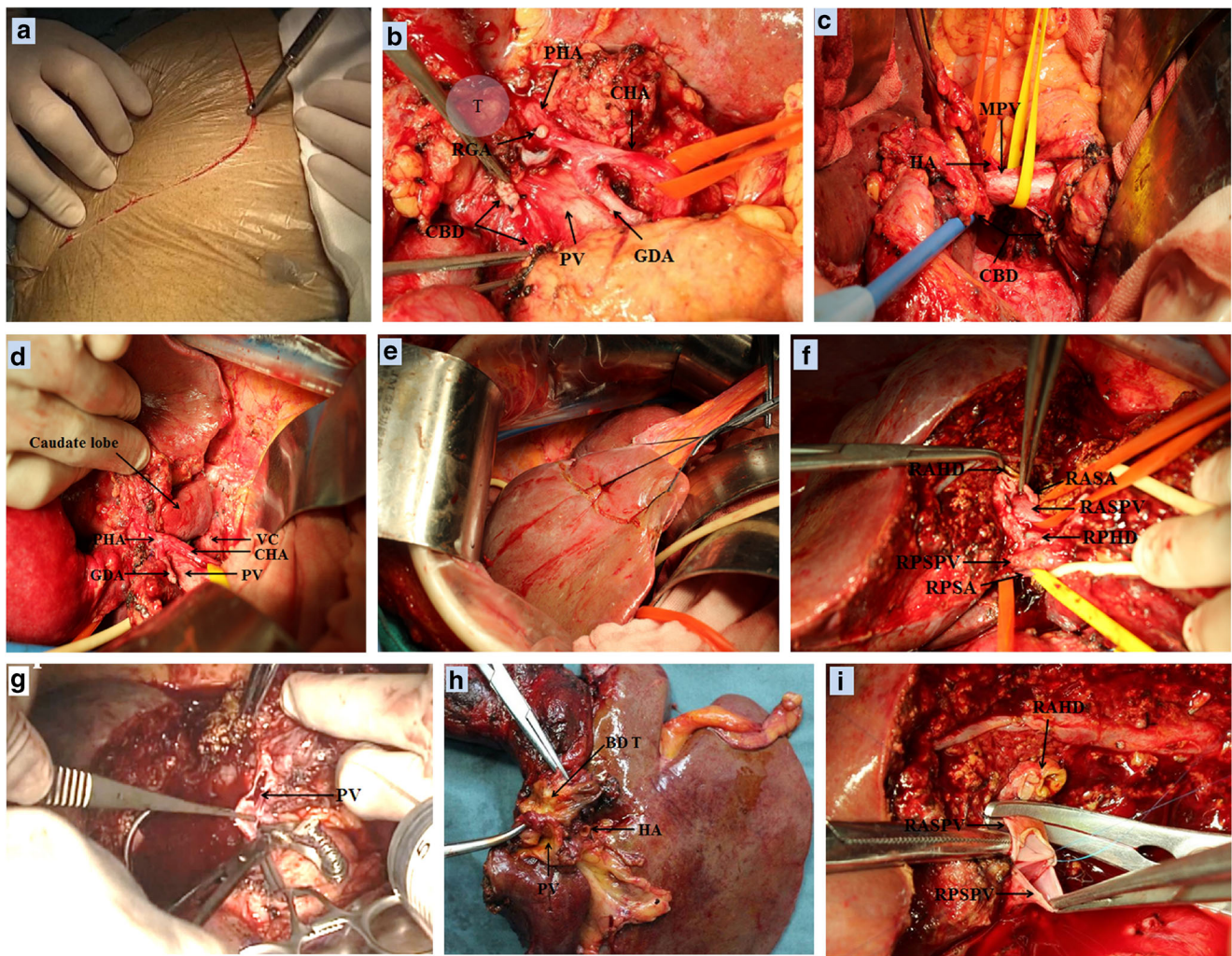


Fig. 1 **a** A right sub-coastal incision like contra-L type. **b** Isolated HA and divided CBD at its entrance into the pancreas. The PV remained to be skeletonized. **c** Isolated MPV. The dissection toward the hilum is stopped in the vicinity of the tumor without attempts to dissect the HA and the PV at the hilum. **d** The left liver and caudate lobe are mobilized from left side to right. **e** Transection line between right and left liver and a rubber catheter passed from retrohepatic tunnel. **f** Isolated RPHD, RASA, RPSA, RASPV, and RPSV with transected RAHD. **g** Transection of

MPV and PHA with scissors under vascular clamping. **h** En bloc resected specimen including left liver, caudate lobe, involved PV and HA, and bile duct tumor (BD T). **i** Vein plasty of RASPV with RPSV. **j** An end-to-end anastomosis of RPV to MPV. **k** Accomplished anastomosis of RASPV and RPSV to MPV and restoring of the portal flow. **l** An end-to-end anastomosis of GDA to RPSV. **m** An arterial-portal shunting of the PHA to RASPV. **n** Biliary plasty of RAHD with RPHD. **o** Hepatojejunostomy by Roux-en-Y anastomosis

stopped in the vicinity of the tumor without attempts to dissect the HA and the PV at the level of the bile duct bifurcation. If possible, the right posterior sectional branches of the HA (RPSA) and the PV (RPSV) are isolated with vessel loops inside the Rouviere's sulcus (Figs. 1b, c and 2b).

Step 3. The left liver and caudate lobe are mobilized from the left to right by dividing the Arantius ligament at its attachment to the root of left hepatic vein. Belgiti's hanging maneuver¹⁵ is used to transect parenchyma along the left side of middle hepatic vein (MHV) or along the right side of MHV in case it has been involved by tumor, to expose the right pedicle

without mobilization of the right liver. The anterior and posterior sectional branches of the right hepatic artery (RHA), the right portal vein (RPV), and the right hepatic duct (RHD) are identified and isolated, respectively (Figs. 1d–f and 2c).

Step 4. The anterior and posterior sectional branches of RHD are then divided first by scissors with great care being taken to avoid an injury to the corresponding arterial branches. At this point, the specimen including the left liver with the caudate lobe and total hilum with tumor and dissected tissues is connected to the right liver only by the HA and PV. After evaluating the lengths of involved vessels that

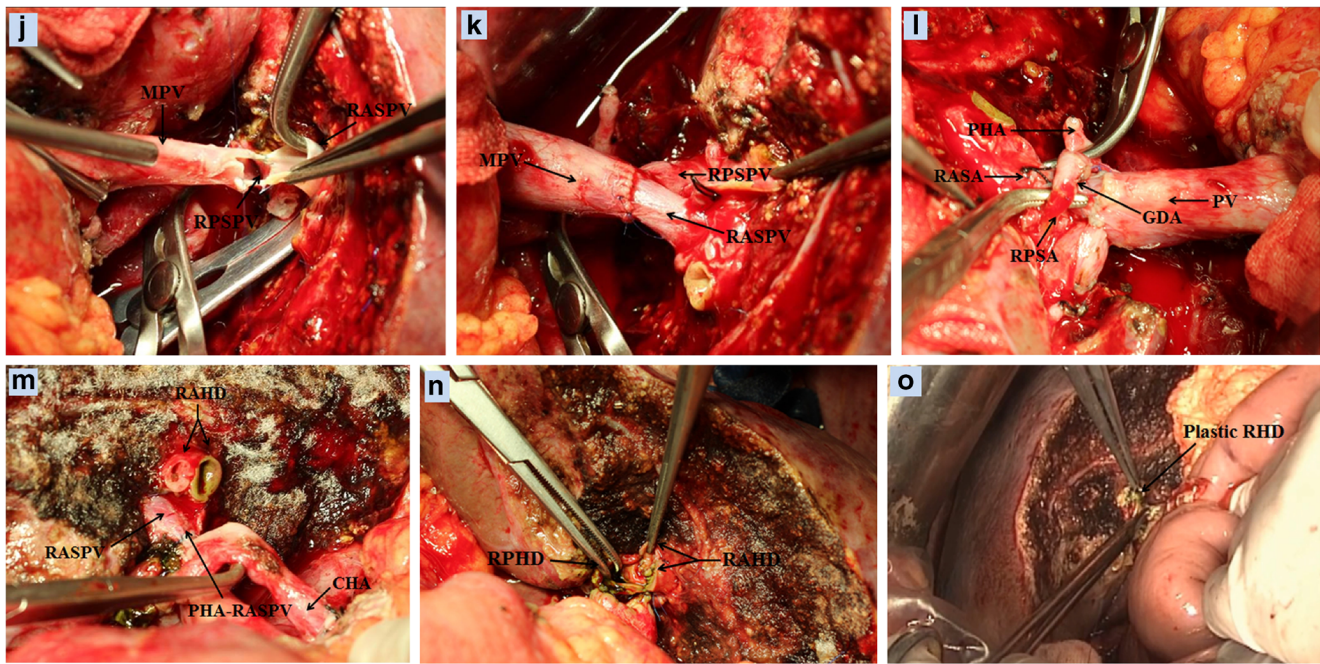


Fig. 1 continued.

need to be resected, the HA and PV are clamped both proximal and distal to the tumor using vascular clamps and divided. The distal division of the HA and the PV is at the points where the anterior and posterior sectional branches of RHA and RPV or the RHA and the RPV *per se* can safely be controlled via vascular clamps. Frozen sections of each of the bile duct margins, if possible, including the cut margins of the PV and the HA, were performed to ensure a radical resection. The dissected specimen is removed immediately (Figs. 1e–h and 2c).

Step 5. Subsequent reconstruction begins with PV by suturing the anterior and posterior sectional branches of PV: RASPV and RPSPV together followed by an end-to-end anastomosis to the MPV or direct end-to-end anastomosis between the remaining RPV and MPV in case there is no invasion of the second-order branches of RPV. After the portal flow to the right liver is restored, an end-to-end anastomosis of right anterior sectional artery (RASA) to PHA and RPSA to GDA is performed under a magnifying scope using a magnification of 2500. If first order of RHA ramification is clear, it may also serve as an alternative for arterial anastomosis to the PHA. Time for hilum clamping (THC) defined as time between PV clamping to restoration of PV flow, as well as time for HA and PV anastomosis, is recorded. Arterio-portal shunting can serve as an alternative in the case of arterial reconstruction failure (Figs. 1i–m and 2d, e).

Step 6. Finally, biliary reconstruction is performed using a Roux-en-Y loop after connecting multiple orifices of bile ducts into one by biliary plasty (Figs. 1n, o and 2f).

Occasionally, tumor invasion is limited to the left-side bifurcation of the MPV and the ramification of PHA, i.e., both the RPV and RHA can be divided extrahepatically with negative margins. The resection and reconstruction of the PV and HA for the right liver can be accomplished prior to hemihepatectomy.

Histology and Statistical Analysis

Histopathologic examinations were performed using AJCC classification system.¹⁶ Microscopic tumor invasion to the PV and HA was classified as grade 0 (no involvement), grade I (cancer invasion limited to the tunica adventitia or media), or grade II (cancer invasion reaching the tunica intima) according to the Nagoya's criteria.⁹ Postoperative complications were classified using the Clavien-Dindo classification.¹⁷ Overall survival (OS) was defined as the time between surgery and death or most recent follow-up. Postoperative mortality was defined as death occurring within hospital stay or within 90 postoperative days. Continuous variables were reported as means with standard deviation or medians with interquartile range (IQR) as deemed appropriate. Categorical variables were reported as whole numbers and percentages. Statistical

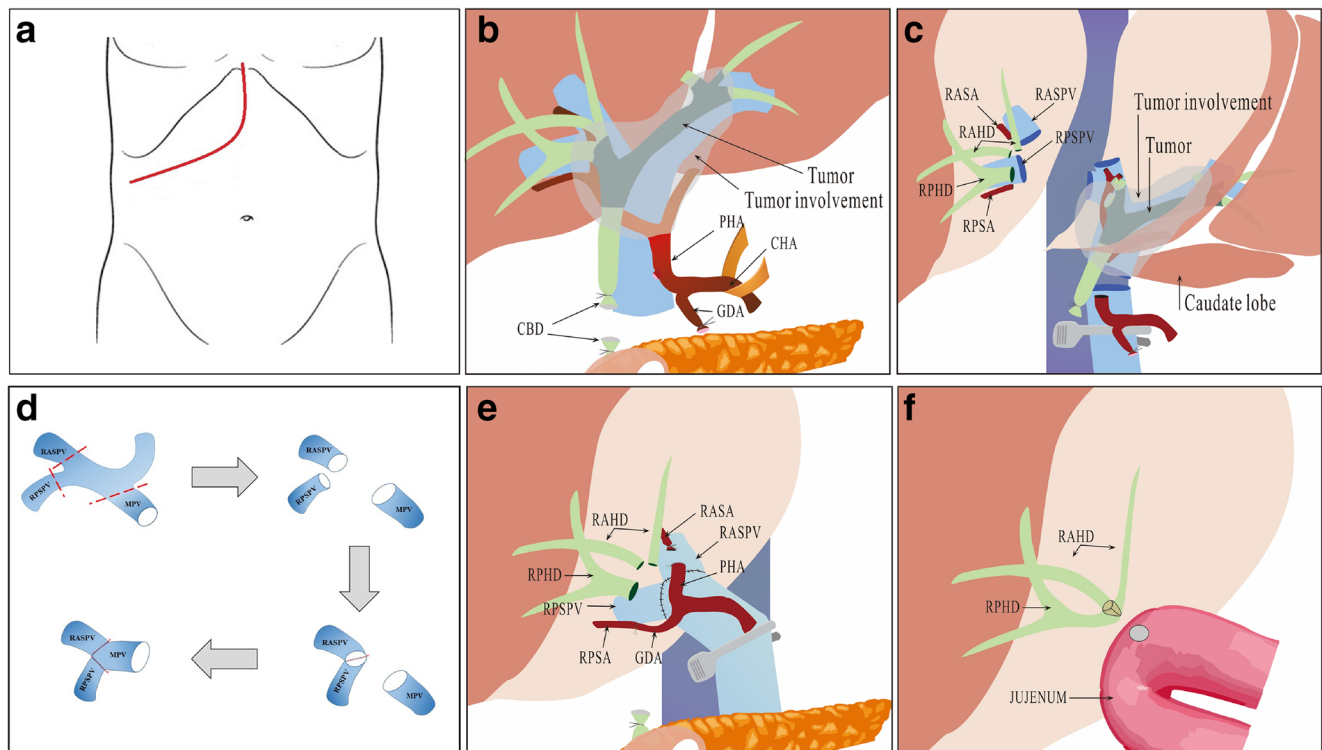


Fig. 2 **a** Incision (diagrammatical representation of Fig. 1a). **b** Tumor location in bile duct and involvement regions of PV and HA (diagrammatical representation of Fig. 1b, c). **c** Transected vessels and bile ducts with en block resected specimen going to be removed (diagrammatical representation of Fig. 1e f, g). **d** Anatomical

representation of the PV resection and reconstruction (diagrammatical representation of Fig. 1i, j, k). **e** Diagrammatical representation of accomplished anastomosis of PV, HA, and arterial-portal shunting of the PHA to RASPV (Fig. 1k–m). **f** Plastic RHD and ready for hepatojejunostomy (diagrammatical representation of Fig. 1n, o)

analyses were carried out using SPSS (SPSS, Inc., Chicago, 16.0).

Results

Eight patients underwent THER-LH. Clinical features and operative data are presented in Table 1. The median age was 64 (IQR 53.25–75.50) years, and four patients were females. The tumors were classified as Bismuth–Corlette type IIIb in three patients and type IV with left-sided predominance in five patients. None of the eight patients received neoadjuvant chemotherapy. Two patients developed PHC with underlying intrahepatic cholelithiasis. One of them (patient 2) had undergone gastrectomy for gastric carcinoma and left lateral sectionectomy for early stage intrahepatic cholangiocarcinoma 2 and 5 years prior to THER-LH, respectively. Another patient (patient 7) had undergone a left lateral sectionectomy due to intrahepatic cholelithiasis 5 years prior to THER-LH. Two patients with total bilirubin more than 200 $\mu\text{mol/l}$ had undergone percutaneous transhepatic biliary drainage (PTBD). Given macroscopic involvement, concomitant organ resections were performed in three patients. One patient each required a pancreatoduodenectomy, gastric antrum resection, and combined gastric antrum and duodenal bulb resection.

The median operative time and estimated blood loss were 520 (IQR 415–630) min and 700 (IQR 425–950) ml, respectively. Because of past history of abdominal surgery and combined pancreatoduodenectomy with clearance of para-aortic lymph nodes and soft tissues, patient 2 has the longest operation time of 870 min. The median length of resected vessel was 3.35 (IQR 1.6–3.5) cm for HA and 3.10 (IQR 1.5–3.5) cm for PV, respectively. Reconstructions were accomplished by an end-to-end anastomosis of RPV stump to MPV in five patients, and by combining anterior with posterior branches of RPV together, and subsequent end-to-end anastomosis to the MPV in three patients (Fig. 1). Reconstruction of the HA was performed after portal flow was restored. In six patients, one artery was reconstructed with an end-to-end anastomosis of RHA to PHA for each. In one patient who had two arterial stumps of RPSA and RASA, an end-to-end anastomosis of RPSA to GDA and an end-to-side anastomosis of PHA to anterior branch of RPV (arterio-portal shunting) with the ligation of RASA were performed. In another patient with RHA coming from the superior mesenteric artery, the aberrant RHA stump was reconstructed using an end-to-end anastomosis to the PHA. The time taken for vessel resection and reconstruction was 25.6 ± 12.3 min for PV and 19.1 ± 4.9 min for HA. Therefore, the mean THC was 27.3 ± 11.9 min (15–41). Postoperatively, serum ALT, AST, and total bilirubin levels

Table 1 Clinical and operative characteristics of patients

Patient no.	Gender	Age (years)	B-C classification	TB (μmol/l)	Tumor size (cm)	Pre-OR BD	Additional OR	OR time (min)	THC (min)	rHA length (cm)	rPV length (cm)
1	M	62	IIIb	183.9	2.0	N	N	390	15	1.5	1.0
2	M	48	IV	20.9	5.0	N	PD	870	38	3.5	3.5
3	M	78	IIIb	127.5	7.0	N	GA	540	16	3.5	3.2
4	F	60	IIIb	13.6	4.5	N	N	500	20	1.5	1.5
5	F	51	IV	173.1	2.5	N	N	380	15	2.0	1.5
6	F	66	IV	27.9	4.0	N	N	540	41	3.5	3.5
7	F	68	IV	334.5	6.0	Y	GA and DB	660	41	3.6	3.5
8	M	78	IV	285.5	3.0	Y	N	490	32	3.0	2.0

were elevated on day 1, but returned to a normal value within 10 days after surgery (Fig. 3). Patients 3 and 7 experienced a Clavien-Dindo grade IVa and II complications, respectively. Patient 7 who had bile leakage classified as grade II¹⁸ was treated with extended drainage, while patient 3 developed intraperitoneal abscess with bleeding required re-laparotomy. There was no perioperative mortality. Histopathologic examination demonstrated that all eight patients had tubular adenocarcinoma with well, moderate, and poor differentiations presented in one, four, and three patients, respectively (Table 2). Perineural involvement was observed in all patients. Microscopic examination of vessels revealed no invasion to both the PV and HA for patient 5 (grade 0) who had marked fibrosis around the resected HA and PV. The extent of PV invasion for other patients was grade I in six and grade II in one. And the extent of HA invasion was grade I in the other seven patients (Fig. 4). Therefore, approximately all of the patients with PV and HA resections appeared to have microscopic invasion except one. Negative bile duct margins were achieved in all patients. The number of harvested nodes was 15.5 (IQR 13.25–17.75), and positive nodes were identified in six patients with periaortic node metastasis of N2 in two patients. As per the AJCC staging system,¹⁶ one patient had

stage IIIb, two patients had stage IVb diseases due to N2 metastasis, and the other five patients had stage IVa diseases (Table 2). The median length of hospital stay was 16.5 (IQR 14.25–20.00) days. On most recent follow-up in March, 2017, three patients developed recurrence and died at 11, 18, and 24 months after surgery, respectively. The remaining patients were alive. The median survival was 24 months with one patient having a disease free survival of 50 months (Table 2).

Discussion

It has been reported that operative macroscopic PV infiltration is a significant prognostic factor.¹⁹ Advancements in surgical techniques has made resection of tumors with PV involvement possible with acceptable morbidity and mortality.^{1–3} However, a systematic review revealed that there were no proven survival advantage with portal vein resection, and arterial resection results in higher morbidity and mortality with no proven benefit.¹ Dissection of bile ducts and tumor off of the PV bifurcation and RHA risks spillage of tumor cells locally, which may contribute to the high rate of local recurrence. Neuhaus et al. advocated en bloc hilar resection using

Fig. 3 Changing lines of serum ALT, AST, and total bilirubin (TB) levels of eight patients after surgery

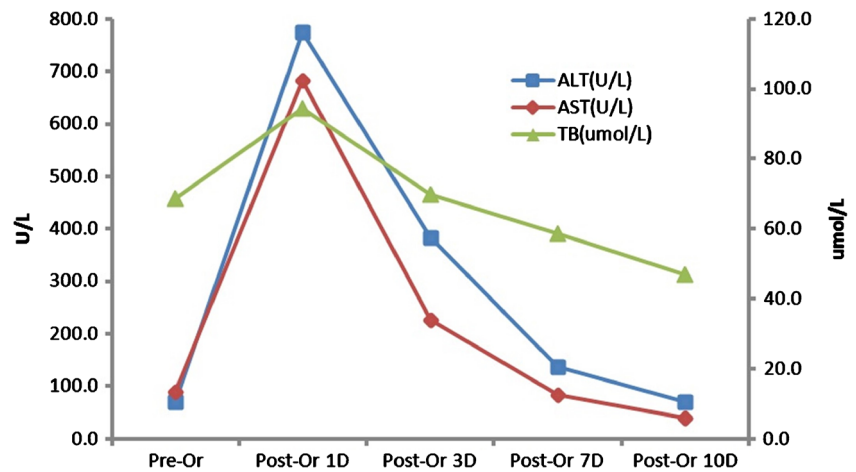


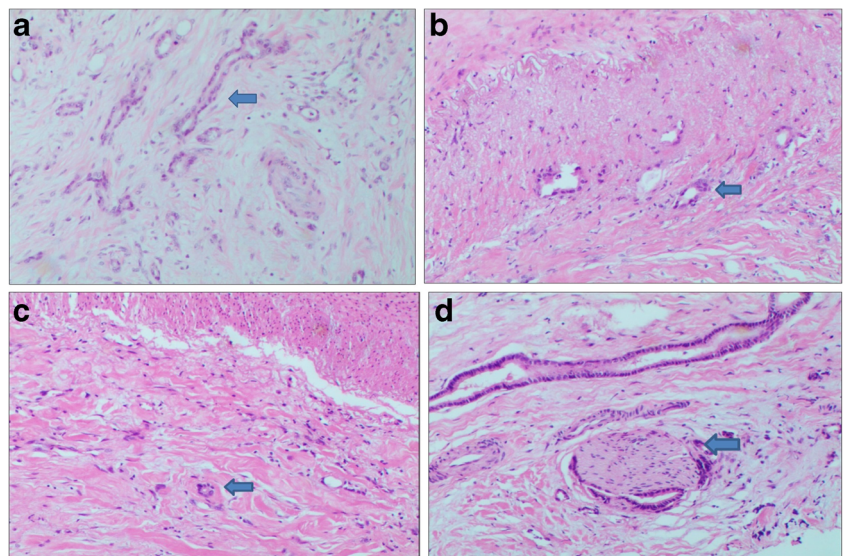
Table 2 Histopathological data and outcomes of patients

Patient no.	Histology	Microscopic invasion of rHA (grade)	Microscopic invasion of rPV (grade)	PLN/TLN	AJCC stage (2010)	Complications ^b	Length of hospital stay (day)	Recurrence (month)	Overall survival
1	Moderate	I	I	0/13	IVA	N	10	N	50 a
2	Moderate	I	I	4/16 ^a	IVB ^a	N	20	18	24 d
3	Poor	I	I	6/14	IVA	Y	17	13	18 d
4	Poor	I	I	2/11	IVA	N	20	N	22 a
5	Moderate	0	0	1/15	IIIB	N	15	N	24 a
6	Well	I	I	0/18	IVA	N	14	N	17 a
7	Poor	I	II	6/21 ^a	IVB ^a	Y	20	7	11 d
8	Moderate	I	I	5/17	IVA	N	16	N	14 a

the no-touch technique for treatment of right-side PHC.¹⁰ More recent data have reported longer survival as compared to that after standard resection for same stage disease.¹¹ However, in principle, hilar en bloc resection for left-sided tumors has never been reported because of the associated morbidity and the mortality associated with routine RHA reconstruction.¹² Anatomically, the RPV is short and bifurcates early on into anterior and posterior branches. Also, the anterior and posterior branches of the RHA become smaller and lack elasticity. The technique of hilar en bloc resection for left-sided tumors is much more difficult than that for right-sided tumors because of the reconstruction of RPV and RHA. Therefore, Neuhaus and Tamoto concluded that hilar en bloc resection is only indicated for right-sided hepatectomies but not feasible for left-sided hepatectomies.^{10,14} Besides, blood flow of both the HA and PV has to be interrupted during hilar en bloc resection with left hepatectomy which can induce ischemic reperfusion liver damage. In order to avoid long-term ischemic injury, Miyazaki et al.²⁰ reported a technique of keeping arterial blood supply intact by initially resecting

and reconstructing the PV with subsequent HA resection and reconstruction. To resect HA and PV separately, the dissection of hilar vessels might be necessary in a manner that does not follow principles of an en bloc resection. Meanwhile, the reconstruction of RPV might be difficult for most of advanced tumors using this approach due to limited space occupied by the being resected specimen. Miyazaki et al. reported 33% mortality and no survivors at 3 years.^{5,20} These poor outcomes could be related to technical difficulty of the anastomosis as well as tumor recurrence. In the last decade, only Nagino et al. have reported a large series on patients undergoing combined HA and PV resection for PHC.⁹ The time taken for vessel resection and reconstruction was 25 ± 19 min for the PV and 119 ± 56 min for the HA. The technique of simultaneous resection of PV and HA was not described in detail. The time of vascular flow interruption of both the HA and PV has not been reported by the same team.^{9,21} We inferred from the long time for HA resection and reconstruction and lack of comment on liver ischemic time that they may employ a technique similar to that described by Miyazaki et al.²⁰

Fig. 4 Histological pictures of tumor for Patient 6. **a** Moderately differentiated hilar cholangiocarcinoma with abundant fibrous stroma. **b** Adenocarcinoma cells invade the outer membrane of hepatic artery. **c** Adenocarcinoma cells invade the smooth muscle of portal vein. **d** Adenocarcinoma cells invade the nerve



By the refinement of surgical technique developed in liver transplantation, we have advocated an aggressive surgical strategy to perform major hepatectomy with simultaneous resection of the PV and HA for the treatment of PHA starting in 2012 and have been able to perform THER-LH for the treatment of eight patients with left-sided PHC from 2013 to 2015. To our knowledge, this is one of the first reports on hilar en bloc resection with left-sided hepatectomy. Our technique of THER-LH is quite different from hilar en block resection proposed by Neuhaus.¹⁰ There are some technical and oncological superiorities of THER-LH over other techniques: (1) preserved volume of right liver is larger than that of the left liver; therefore, preoperative portal vein embolization (PVE) is rarely required; (2) perineural invasion and lymphangial carcinomatosis can frequently be observed up to 2 cm from the tumor into the liver and HDL, and the resection of hilar structures including HA and PV by THER-LH provides three-dimensional resected safety margins with maximized oncological dissection; (3) given that RPV is short or bifurcates early, its dissection is easier after exposure of right pedicle, making an end-to-end anastomosis of PV more feasible; (4) with the help of Belgiti's maneuver, liver parenchyma transection becomes easier without mobilization of the right liver which benefits protection of collateral circulation. When performing this technique, we observed a rich retrograde blood flow from the distant ends of the transected vessels.

The interruption of the blood flow during THER-LH can induce ischemic liver damage. Clinical studies have established 60 min as the safe duration under normthermic conditions.^{22–24} To reduce the ischemic time, we performed the PV resection lastly and reconstruction immediately after removing the specimen. This procedure was accomplished within 40 min in our study. The duration of hilum clamping in our patients was 27.3 ± 11.9 min (15–41). The serum enzymes and bilirubin levels returned to near normal range within 10 postoperative days suggesting that the ischemic effect on liver was minimal.

Jarnagin et al.²⁵ had proposed a criterion of non-resectability in patients with PHC that included local factors such as encasement or occlusion of the main PV proximal to its bifurcation and atrophy of one lobe with encasement of contralateral PV branch. The extent of disease of the reported eight patients is within these criteria; however, an R0 resection was achieved safely, resulting in a median survival of 24 months with one patient being disease free at 50 months after surgery. Therefore in our opinion, the technique of THER-LH can have a significant impact on the revision of guidelines for the treatment of PHC.

In conclusion, we believe that the THER-LH is safe and feasible and can have some benefit in terms of the prognosis of these patients. However, due to the limited number of patients and short follow-up, further studies are required to determine

the true oncological superiority of this novel approach for the treatment of advanced PHC.

B-C Bismuth-Corlette classification, *TB* total bilirubin, *OR* operation, *N* no, *Y* yes, *THC* time of hilum clamping, *rHA* resected hepatic artery, *rPV* resected portal vein, *Pre-OR BD* preoperative biliary drainage, *PD* pancreatoduodenectomy, *GA* gastric antrum resection, *DB* duodenal bulb resection

Grade 0: no involvement; grade I: invasion limited to the tunica adventitia or media; grade II: invasion reaching to the tunica intima

rHA resected hepatic artery, *rPV* resected portal vein, *PLN* positive lymph nodes, *TLN* number of harvested lymph nodes, *a* alive, *d* dead

^aN2 metastasis¹⁶

^bGrand II or more according to Clavien-Dindo Classification of Surgical Complications¹⁷

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