Journal of Gastrointestinal Surgery (2019) 23:1443–1453
https://doi.org/10.1007/s11605-018-3948-x

ORIGINAL ARTICLE

Surgical Outcomes for Perihilar Cholangiocarcinoma with Vascular Invasion

Ryota Higuchi[1] · Takehisa Yazawa[1] · Shuichiro Uemura[1] · Wataru Izumo[1] · Takehiro Ota[2] · Kosuke Kiyohara[3] · Toru Furukawa[4] · Hiroto Egawa[1] · Masakazu Yamamoto[1]

Received: 14 June 2018 / Accepted: 23 August 2018 / Published online: 10 September 2018

Abstract

Purpose To investigate short- and long-term surgical outcomes for patients with perihilar cholangiocarcinoma and vascular invasion.

Methods Data from 249 patients who underwent perihilar cholangiocarcinoma surgery between 2000 and 2016 were retrospectively analyzed. Patient evaluations included short-term surgical outcomes following vascular resection and long-term outcomes in cases with histopathological vascular invasion.

Results Mortality was 3.6% overall; 16% for hepatic artery resections, 5.4% for portal vein resections, and 1.7% in the absence of vascular resection ($p = 0.029$). No between-group differences were observed in the incidence of Clavien–Dindo grade ≥ 3 complications. The factors related to perioperative mortality were hepatic artery resection (odds ratio [OR] = 25.5), right trisectionectomy (OR = 13.0), and central bisectionectomy (OR = 13.8). Multivariate analysis for overall survival identified several prognostic factors: carcinoembryonic antigen level ≥ 5 ng/mL (hazard ratio [HR] = 1.68), poor differentiation (HR = 2.39), distant metastasis (HR = 1.97), and R1 invasive resection (HR = 2.13). Five-year overall survival for patients with portal vein invasion and M0R0/1cis was 35.6%, significantly worse than the 53.4% for patients with no portal vein invasion and M0R/1cis but better than the 0% for patients with portal vein invasion and M1 or R1. Those with hepatic arterial invasion and M0R0/1cis were 24.7%, significantly worse than the 53.4% for patients with no hepatic arterial invasion and M0R0/1cis but significantly better than the 0% for patients with hepatic arterial invasion and M1 or R1.

Conclusion Short-term outcomes for patients with perihilar cholangiocarcinoma and undergoing vascular resection were poor compared to those without vascular resection. Long-term survival in R0M0 disease was more favorable; aggressive surgery is recommended.

Keywords Perihilar cholangiocarcinoma · Survival · Surgical treatment

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11605-018-3948-x) contains supplementary material, which is available to authorized users.

✉ Masakazu Yamamoto
yamamoto@ige.twmu.ac.jp

[1] Department of Surgery, Institute of Gastroenterology, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan

[2] Department of Surgery, Ebara Hospital, 4-5-10 Higashiyukigaya, Ota-ku, Tokyo 145-0065, Japan

[3] Department of Food Science, Faculty of Home Economics, Otsuma Women's University, 12 Sanbancho, Chiyoda-ku, Tokyo 102-8357, Japan

[4] Department of Histopathology, Tohoku University Graduate School of Medicine, 2-1 Seiryomachi, Aoba-ku, Sendai 980-8575, Japan

Abbreviations

PHC	Cholangiocarcinoma
HAR	Hepatic artery resection
PVR	Portal vein resection
NVR	No vascular resection
HAI	Histopathological hepatic arterial invasion
aHAI	Absence of histopathological hepatic arterial invasion
PV	Portal vein
PVI	Histopathological portal vein invasion
aPVI	Absence of histopathological portal vein invasion
NVI	No vascular invasion
CA	Cancer antigen
CEA	Carcinoembryonic antigen
OR	Odds ratio

HR	Hazard ratio
M0	Distant metastasis-negative
M1	Distant metastasis-positive
R0	Negative surgical margin
R1cis	High-grade dysplasia/carcinoma in situ of the bile duct margin
R1	Bile duct stump-positive cases with invasive cancer
OS	Overall survival
PD	Pancreaticoduodenectomy
PPPD	Pylorus-preserving PD
POD	Postoperative day

Introduction

In recent years, vascular resection and reconstruction negative surgical margin (R0) surgeries for patients with perihilar cholangiocarcinoma (PHC) have become acceptable in some specialized facilities and are actively performed for improving surgical outcomes.[1–4] In a clinical practice guideline, combined portal vein resection (PVR) is recommended for patients with histopathological portal vein invasion (PVI) because the prognosis for patients treated with PVR is significantly better than that for patients treated without resection. However, the clinical benefits of combined hepatic arterial resection (HAR) for patients with histopathological hepatic arterial invasion (HAI) are controversial, with no recommendations currently published.[5] Also, as for vascular resection for PHC, surgical morbidity and mortality numbers remain high in some facilities.[6–10] Moreover, studies employing multivariate analyses of both surgical mortality associated with vascular resection and outcomes in patients with vascular invasion are very limited. Thus, the indications for and significance of vascular resection and reconstruction for PHC remain controversial.

Therefore, this study aimed to investigate the safety and significance of vascular resection and reconstruction for PHC at our institute, examining both short- and long-term surgical outcomes.

Materials and Methods

Study Design and Subjects

This study was approved by the institutional review board of Tokyo Women's Medical University (approval number 4328); the need for informed consent was waived because this was a retrospective chart review analysis. This retrospective investigation involved the 249 consecutive patients who underwent surgery for PHC at our hospital between 2000 and 2016. There were no exclusion criteria in effect during patient selection. The short-term surgical outcomes for patients following HAR, PVR, or no vascular reconstruction (NVR) and the long-term outcomes for patients with HAI, PVI, or no vascular invasion (NVI) were examined. The median age of the patients was 70 years, and 71% were male; most patients were classified as having tumor types greater than Bismuth III (86%, 214/249). Right hepatectomy was performed in 41% of the patients, and left hepatectomy was performed in 38%; simultaneous pancreaticoduodenectomy (PD) was performed in 3% of the patients.

Surgical Policy

PVR and HAR were only performed if invasion was suggested by the intraoperative findings.

PVR was performed in 28% (69/249) of the patients, with circular and wedge resections performed in 83% (57/69) and 17% (12/69) of the patients, respectively; interposition grafts were not required. Ten patients undergoing circular resection and two undergoing wedge resection also underwent simultaneous HAR; therefore, these cases were included in the HAR group (Table 1). PVR was performed before hepatectomy in 15 patients, during hepatectomy in 45 patients,[11] and after hepatectomy in 7 patients; the order was not recorded for two patients.

HAR was performed in 8% (19/249) of the patients, involving circular resection in all cases. The first two reconstructions were performed by a general surgeon using surgical microscope guidance, and the remaining procedures were performed by a plastic surgeon also under surgical microscope guidance. Right HAR ($n = 18$) was performed in 15 patients undergoing left hepatectomies and in individual patients undergoing left trisectionectomy, central bisectionectomy, and segment 1 liver resection involving pylorus-preserving PD (PPPD). Left HAR ($n = 1$) was performed in one case of right hepatectomy and was reconstructed using the right gastric artery. In the other 18 right HAR cases, the proper hepatic artery was used for 7, the gastroduodenal artery for 4, the right hepatic artery for 4, and the right gastroepiploic artery, middle colic artery, and left hepatic artery for 1 case each. HAR was performed during hepatectomy in 4 patients and after hepatectomy in 14 patients; the order was not recorded for all patients. All procedures were performed using end-to-end anastomosis, without interposition grafts. Intra- or postoperative anticoagulation therapy was not performed.

All procedures involved regional lymph node dissection, including the pericholedochal, retroportal, cystic duct, right celiac, posterior superior, pancreatoduodenal, and perihepatic arterial nodes. When there was evidence of swelling, specimens from the paraaortic lymph nodes were also evaluated. Since 2005, major hepatectomy has been primarily indicated for the majority of PHC patients. Before that, some patients with Bismuth type 1 or 2 tumors, without vascular invasion, underwent limited resections, depending on tumor extension and/or patient condition.[12] Until intrahepatic cholangiocarcinoma with hepatic hilar invasion was categorized as perihilar

Table 1 Background, surgical morbidity, and mortality rate comparisons among patients undergoing NVR, PVR, and HAR

	NVR $n = 174$	PVR $n = 56$	HAR $n = 19$	p value[b]
Age, years, median	70.0	69.5	67.0	0.16[a]
Males	126 (72%)	38 (68%)	13 (63%)	0.76
CA19.9, U/mL, median	55.5	138	353	**0006**[a]
CEA, ng/mL, median	2.5	3.1	2.0	0.18[a]
Jaundice**	104(60%)	40 (71%)	16 (84%)	0.052
Biliary drainage				**0.005**[c]
ENBD	62 (36%)	31 (55%)	4 (21%)	**0.009**
PTBD	62 (36%)	18 (32%)	12 (63%)	0.051
WD	50 (28%)	7 (13%)	3 (16%)	**0.028**
PVE	11 (6.3%)	11 (20%)	1 (5.3%)	**0.015**
Bismuth 4	54 (31%)	28 (50%)	8 (42%)	**0.032**
Hepatectomy type				**< 0001**[e]
R2	65 (37%)	36 (64%)	1 (5%)	**< 0001**
R3	7 (4%)	4 (7%)	0	0.50
L2	68 (39%)	13 (23%)	14 (74%)	**< 0001**
L3	5 (3%)	2 (4%)	1 (5%)	0.57
C2	5 (3%)	1 (2%)	1 (5%)	0.64
other	24 (14%)	0	2 (10%)	**0.003**
PD	3 (2%)	4 (7%)	1 (5%)	0.066
Blood loss, mL, median	1234	1364	1580	0.058[a]
Operative time, min, median	389	415	520	**< 0001**
Morbidity (CD ≥ 3)	58 (33%)	25 (45%)	9 (47%)	0.19
Vascular complications	5 (3%)	7 (13%)	5 (26%)	**< 0001**[d]
Pseudoaneurysms	1 (0.6%)	0	2 (11%)	**0.038**
Reconstructed HA problems	0	0	2 (11%)	**0.006**
Intraabdominal bleeding	3 (1.7%)	1 (1.8%)	1 (5.3%)	0.39
PV stenosis	0	1 (1.8%)	0	0.30
PV thrombus	1 (0.6%)	5 (8.9%)	0	**0.004**
Mortality	3 (1.7%)	3 (5.4%)	3 (16%)	**0.009**
R				0.36[c]
R0	115 (66%)	35 (63%)	12 (63%)	0.86
R1 cis	22 (13%)	7 (13%)	0	0.30
R1	37 (21%)	14 (25%)	7 (37%)	0.25
AJCC T3/4	88 (51%)	50 (89%)	16(84%)	**< 0001**
AJCC N1/2	76 (44%)	33 (59%)	13 (68%)	**0.033**
AJCC M1	19 (11%)	7 (13%)	2 (11%)	0.94

The data in bold shows significant p value

HAR group includes patients with both HAR and PVR ($n = 13$)

NVR no vascular resection, *PVR* portal vein resection, *HAR* hepatic artery resection, *CA* cancer antigen, *CEA* carcinoembryonic antigen, *ENBD* endoscopic naso-biliary drainage, *PTBD* percutaneous transhepatic biliary drainage, *WD* without drainage, *PVE* portal vein embolization, *PD* pancreatoduodenectomy, *CD* Clavien–Dindo classification, *HA* hepatic artery, *PV* portal vein, *R1-cis* bile duct stump-positive cases with residual high-grade dysplasia/carcinoma in situ, *R1* bile duct stump-positive cases with invasive cancer, with or without other residual cancers, *AJCC* American Joint Committee on Cancer

[a] Kruskal–Wallis rank sum test

[b] Fisher's exact test for count data (2 × 3)

[c] Fisher's exact test for count data (3 × 3)

[d] Fisher's exact test for count data (5 × 3)

[e] Fisher's exact test for count data (6 × 3)

[f] Jaundice, serum total bilirubin ≥ 2.0 mg/dL

cholangiocarcinoma, in 2014,[13] patients with intrahepatic cholangiocarcinoma underwent resection; however, these patients also had distant metastasis, such as intrahepatic metastasis or distant lymph node metastasis.

Pathological Examination

Formalin-fixed paraffin-embedded tissue sections were examined histologically, according to the TNM classification system of the American Joint Committee on Cancer[14] and the General Rules for Surgical and Pathological Studies on Cancer of the Biliary Tract of the Japanese Society of Biliary Surgery,[15] and included observations regarding primary tumor status, lymph node involvement, and histopathological grade. All pathological specimens were re-checked for invasion of the hepatic artery and portal vein by a pathologist.

Adjuvant Chemotherapy

Adjuvant chemotherapy, defined as the postoperative administration of titanium silicate-1 or gemcitabine within the first 12 weeks, was performed when judged appropriate by the attending physician in patients with lymph node metastases, residual cancer, and good postoperative condition.

Statistics

Between-group differences in the qualitative and quantitative variables were determined using Fisher's exact (two-sided) and the Kruskal–Wallis rank sum tests. Univariate and multivariate analyses were performed using a logistic regression model to determine independent predictors of hospital mortality in patients with PHC. Survival analyses were performed using the Kaplan–Meier method, log-rank test, and Cox proportional hazards model. Only factors that were significant in the univariate analysis were used in the multivariate analysis. All statistical analyses were performed using R, version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria). A p value < 0.05 was considered statistically significant.

Results

Short-Term Surgical Outcomes After Surgery with PVR

Three hospital deaths occurred; however, none were associated with problems due to the actual PVR. Portal vein (PV) thrombi occurred in five patients (Table 1). One patient with an internal hernia had PV thrombus due to a twisted PV. He underwent internal hernia repair and thrombectomy on postoperative day (POD) 6. The second patient had PV thrombus associated with the contact drain and underwent thrombectomy on POD 7. The third patient had PV thrombus due to a twisted PV associated with pancreatitis on POD 6. He underwent thrombectomy and re-reconstruction. The fourth patient developed PV thrombus due to an unknown cause on POD 7 and was treated with anticoagulant therapy. The final patient developed PV thrombus immediately after surgery, due to a narrow PV, and underwent thrombectomy and re-reconstruction. Fortunately, all patients were discharged on PODs 69, 36, 40, 29, and 25, respectively.

Short-Term Surgical Outcomes After Surgery with HAR

Three HAR-related hospital deaths occurred. Obstruction of the reconstructed vessel occurred in two patients. The patient underwent segment 1 resection with PPPD, as well as HAR of the right hepatic and middle colic artery. The next patient underwent left hepatectomy, with liver segment 1 and bile duct resection, and HAR of the right and proper hepatic artery. These reconstructions were performed by a general surgeon, not a plastic surgeon. Subsequently, HAR was performed by plastic surgeons at our institute. The final patient underwent central bisectionectomy with PVR (wedge) and HAR of the posterior section and proper hepatic artery. Once reconstructed, but after hepaticojejunostomy, the anastomoses were injured due to excessive tension by a second surgeon and re-anastomosis was impossible. Eventually, these three patients died on PODs 43, 5, and 15, respectively.

Background, Surgical Morbidity, and Mortality Rates Among NVR, HAR, and PVR Patients

NVR was required in 174 patients (70%), whereas 56 patients (22%) underwent PVR and 19 (8%) underwent HAR (8%, Table 1).

Right hepatectomy was more commonly performed in the PVR group than in the NVR or HAR groups, and left hepatectomy was more commonly performed in the HAR group than in the NVR or PVR groups. Blood losses and operative times were higher in the HAR group than in the NVR and PVR groups. The rate of T3/T4 Tclassifications and N1/2 Nclassifications were significantly higher in the PVR and HAR groups than in the NVR group. The mortality rate was highest in the HAR group (16%), followed by the PVR (5.4%) and NVR (1.7%) groups. The rates of pseudoaneurysm formation and reconstructed HA problems were higher in the HAR group than in the NVR group. The incidence of PV thrombus was higher in the PVR group than in the NVR group. The overall incidence of vascular-related complications was significantly higher in the HAR and PVR groups than in the NVR group.

Multivariate analysis showed that HAR (odds ratio [OR] = 25.5), right trisectionectomy (OR = 13.0), and central bisectionectomy (OR = 13.8) were independent prognostic risk factors for perioperative mortality (Table 2).

Long-Term Surgical Outcomes in Patients with Vascular Invasion

Of the 249 patients, 140 (56%) died from the original disease and 34 (14%) from other causes; at the last follow-up, 11 patients (4%) had survived with recurrence and 64 (26%) were alive and disease-free.

NVI was observed in 129 patients (52%), whereas PVI was observed in 85 patients (34%) and HAI in 35 (14%, Supplemental Table 1, the HAI group includes patients with both HAI and PVI ($n = 27$)). In a comparison among the three groups, PVI and HAI were associated with more advanced disease than was NVI.

The 5-year OS rates were 45.8, 21, and 14.5% in the NVI, PVI, and HAI groups, respectively. Multivariate analysis showed that carcinoembryonic antigen level (OR = 1.68), poor differentiation (OR = 2.39), distant metastasis (OR = 1.97), and residual invasive cancer (R1, OR = 2.13) were independent prognostic risk factors of OS (Table 3). The PVI and HAI rates were similar.

Stratification was performed using factors that were significant in the multivariate analysis and clinically easy-to-use (Fig. 1). The 5-year survival rate in patients with PVI, distant metastasis-negative (M0), and negative or high-grade dysplasia/carcinoma in situ surgical margins (R0/1cis) was 35.6%, which was significantly worse than the 53.4% for

Table 2 Univariate and multivariate analyses of hospital mortality in patients undergoing surgery for perihilar cholangiocarcinoma

		No.	Mortality	Univariable analysis		Multivariable analysis	
				Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value
Period	2000–2008	132	4 (3.0%)	1.0 (ref)	0.60		
	2009–2016	117	5 (4.3%)	1.43 (0.37–5.89)			
Age	< 75 years	189	7 (3.7%)	1.0 (ref)			
	≥ 75 years	60	2 (3.3%)	0.90 (0.13–3.83)	0.89		
Sex	M	177	5 (2.8%)	1.0 (ref)			
	F	72	4 (5.6%)	2.02 (0.49–7.87)	0.30		
Jaundice	No	89	2 (2.2%)	1.0 (ref)			
	Yes	160	7 (4.4%)	1.99 (0.47–13.6)	0.40		
Drainage	WD	60	1 (1.7%)	1.0 (ref)			
	ENBD	96	3 (3.1%)	1.90 (0.24–39.0)	0.58		
	PTBD	92	5 (5.4%)	3.39 (0.53–65.8)	0.27		
PVE	No	226	8 (3.5%)	1.0 (ref)			
	Yes	23	1 (4.3%)	1.24 (0.07–7.22)	0.84		
Bismuth 4	No	159	3 (1.9%)	1.0 (ref)			
	Yes	90	6 (6.7%)	3.71 (0.95–18.0)	0.068		
PVR	0	180	5 (2.8%)	1.0 (ref)			
	1	69	4 (5.8%)	2.15 (0.52–8.38)	0.26		
HAR	0	230	6 (2.6%)	1.0 (ref)		1.0 (ref)	
	Yes	19	3 (16%)	7.0 (1.38–29.3)	<u>0.010</u>	25.5 (2.95–297)	<u>0.004</u>
Hepatectomy	R2	102	2 (2.0%)	1.0 (ref)		1.0 (ref)	
	R3	11	2 (18%)	11.1 (1.22–102)	<u>0.023</u>	13.0 (1.39–125)	<u>0.017</u>
	L2/3	103	1 (1.0%)	0.49 (0.02–5.20)	0.56	0.13 (0.004–1.96)	0.17
	CB	7	2 (29%)	20.0 (2.07–199)	<u>0.006</u>	13.8 (1.03–161)	<u>0.031</u>
	Other	26	2 (7.7%)	4.17 (0.48–36.2)	0.16	2.45 (0.20–24.5)	0.43
PD	No	241	8 (3.3%)	1.0 (ref)			
	Yes	8	1 (12.5%)	4.16 (0.21–27.8)	0.21		
Blood loss	< 1500 mL	160	3 (1.9%)	1.0 (ref)			
	≥ 1500 mL	89	6 (6.7%)	3.78 (0.97–18.3)	0.065		
Surgery time	< 480 min	182	4 (2.2%)	1.0 (ref)			
	≥ 480 min	67	5 (7.5%)	3.59 (0.92–14.9	0.063		

CI confidence interval, *WD* without drainage, *ENBD* endoscopic naso-biliary drainage, *PTBD* percutaneous transhepatic biliary drainage, *PVE* portal vein embolization, *PVR* portal vein resection and reconstruction, *HAR* hepatic artery resection and reconstruction, *R2* right hepatectomy, *R3* right trisectionectomy, *L2* left hepatectomy, *L3* left trisectionectomy, *CB* central bisectionectomy, *PD* pancreatoduodenectomy

Table 3 Univariate and multivariate analyses of overall survival in patients with perihilar cholangiocarcinoma

		Univariate				Multivariate	
		n	OS		*p* value[a]	Hazard ratio (95% CI)	*p* value[b]
			2 years	5 years			
Period	2000–2008	132	60.3	32.5	0.98		
	2009–2016	117	58.8	33.3			
Age, years	< 75	189	59.3	32.3	0.63		
	≥ 75	60	60.5	36.4			
Sex	Male	177	58.5	28.2	**0.037**	1.0	
	Female	72	62.0	45.3		0.81 (0.56–1.17)	0.26
CA19-9, U/L	< 38	83	75.7	51.8	**< 0.001**	1.0	
	≥ 38	166	51.4	23.5		1.47 (0.99–2.17)	0.057
CEA, ng/mL	< 5	204	66.0	38.1	**< 0.001**	1.0	
	≥ 5	44	31.2	11.4		1.68 (1.10–2.56)	**0.016**
Preoperative jaundice	No	89	69.4	45.3	**0.006**	1.0	
	Yes	160	54.3	26.4		1.19 (0.67–2.10)	0.56
Type of drainage	WD	60	63.3	40.2	**0.031**	1.0	
	ENBD	96	65.5	42.0		0.96 (0.50–1.84)	0.91
	PTBD	92	51.5	21.6		1.02 (0.51–2.05)	0.94
Bismuth	1–3	159	63.4	37.3	**0.013**	1.0	
	4	90	52.7	25.2		0.96 (0.69–1.35)	0.82
PVE	No	226	59.2	33.4	0.98		
	Yes	23	63.6	30.0			
Hepatectomy					0.83		
	R2	102	63.1	30.2			
	R3	11	51.9	41.6			
	L2	95	58.7	34.2			
	L3	8	46.9	0			
	CB	7	57.1	57.1			
	other	26	57.0	36.7			
PD	No	241	59.5	32.7	0.41		
	Yes	8	62.5	62.5			
PVI	No	136	73.1	44.7	**< 0.001**	1.0	
	Yes	113	43.1	19.3		1.46 (0.52–4.14)	0.48
HAI	No	214	63.4	36.0	**< 0.001**	1.0	
	Yes	35	36.4	16.0		1.30 (0.79–2.13)	0.31
Blood loss, mL	< 1500	160	67.1	37.9	**0.014**	1.0	
	≥ 1500	89	46.1	24.9		1.24 (0.88–1.74)	0.22
Surgery time, min	< 480	182	62.5	36.4	0.075		
	≥ 480	67	51.9	24.5			
Histology	pap	25	84.0	58.6	**< 0.001**	1.0	
	tub1,2	186	60.5	32.1		1.33 (0.66–2.66)	0.42
	tub3	29	34.5	19.2		2.39 (1.09–5.25)	**0.030**
	other	8	43.8	14.6		1.82 (0.60–5.54)	0.29
AJCC T 8th	1/2	129	74.0	45.4	**< 0.001**	1.0	
	3/4	120	43.8	19.9		1.14 (0.38–3.41)	0.81
AJCC N 8th	0	127	74.5	45.1	**< 0.001**	1.0	
	1	77	47.8	26.7		1.34 (0.92–1.95)	0.12
	2	45	37.3	5.06		1.34 (0.82–2.20)	0.24

Table 3 (continued)

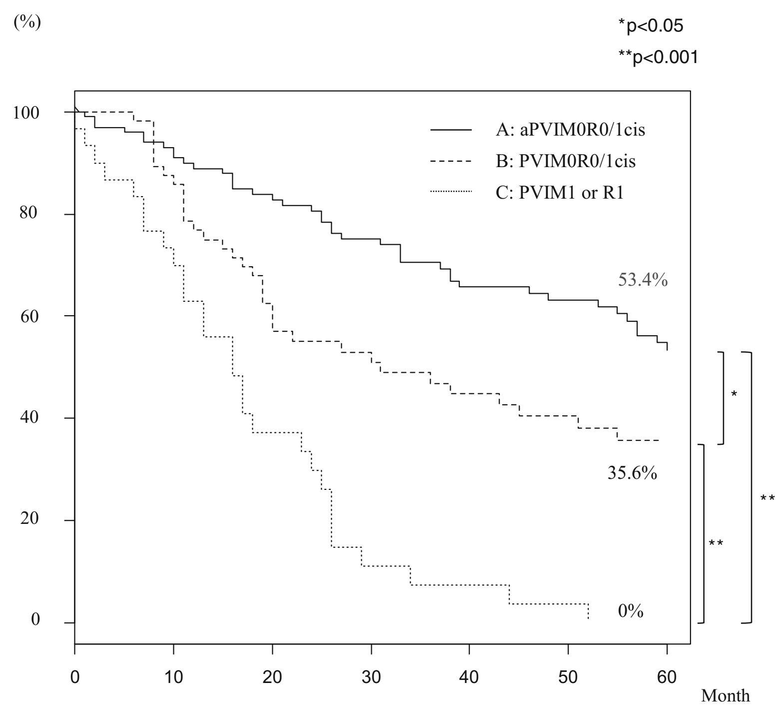
		Univariate				Multivariate	
		n	OS		*p* value[a]	Hazard ratio (95% CI)	*p* value[b]
			2 years	5 years			
AJCC M 8th	0	221	63.3	36.7	**< 0.001**	1.0	
	1	28	28.8	4.11		1.97 (1.19–3.26)	**0.008**
Residual cancer	R0	162	66.7	42.8	**< 0.001**	1.0	
	R1 cis	29	68.5	31.8		1.24 (0.73–2.11)	0.42
	R1	58	35.6	8.00		2.13 (1.44–3.17)	**< 0.001**
Clavien–Dindo classification	≤ 2	157	63.4	40.6	**< 0.001**	1.0	
	≥ 3	92	52.8	20.2		1.32 (0.94–1.85)	0.11
Adjuvant chemotherapy	Absent	145	54.1	32.5	0.20		
	Present	103	67.1	34.1			

The data in bold shows significant *p* value

OS overall survival, *CA* cancer antigen, *CEA* carcinoembryonic antigen, *CI* confidence interval, *WD* without drainage, *ENBD* endoscopic naso-biliary drainage, *PTBD* percutaneous transhepatic biliary drainage, *PVE* portal vein embolization, *R2* right hepatectomy, *R3* right trisectionectomy, *L2* left hepatectomy, *L3* left trisectionectomy, *CB* central bisectionectomy, *PD* pancreatoduodenectomy, *PVI* histopathological portal vein invasion, *HAI* histopathological portal vein invasion, *AJCC* American Joint Committee on Cancer, *R0* curative margin-free resection, *R1-cis* bile duct stump-positive cases with residual high-grade dysplasia/carcinoma in situ, *R1* bile duct stump-positive cases with invasive cancer with or without any other residual cancer

[a] Log-rank test

[b] Cox proportional hazards model



Tumor type	Number at risk	2 years	5 years
aPVIM0R0/1cis	99	76	38
PVIM0R0/1cis	56	28	14
PVIR1 or M1	30	9	0

Fig. 1 Overall survival rates, based on the presence or absence of histopathological portal vein invasion (PVI, aPVI) in patients with distant metastasis-negative (M0) tumors, and negative or high-grade dysplasia/carcinoma in situ surgical margins (R0/1cis), distant metastasis-positive (M1), or bile duct stump-positive cases with invasive cancer (R1). The median survival time was not determined for NPVIM0R0/1cis patients but was 31 months in PVIM0R0/1cis patients and 16 months in PVIM1 or R1 patients.*$p < 0.05$, **$p < 0.001$. PVI, presence of histopathological portal vein invasion; aPVI, absence of histopathological portal vein invasion; M1, distant metastasis; R0, negative surgical margin; R1cis, high-grade dysplasia/carcinoma in situ of the bile duct margin; R1, bile duct stump-positive cases with invasive cancer, with or without any other residual cancer; NS, not significant

those with absence of PVI (aPVI) and M0R0/1cis and significantly better than the 0% of patients with PVI, distant metastasis-positive (M1), or bile duct stump-positive cases with invasive cancer (R1). Similarly, the 5-year survival rate in patients with HAIM0R0/1cis was 24.7%, which was significantly worse than the 53.4% for those with absence of hepatic arterial invasion (aHAI) and M0R0/1cis and better than the 0% of those with HAIM1 or R1 ($p < 0.001$).

The 5-year OS was not significant in patients with PVIM0R0/1cis, with or without PVR, or in those with HAIM0R0/1cis, with or without HAR; there were no long-term survivors of HAIM0R0/1cis who underwent HAR (Supplemental Figs. 1 and 2).

Discussion

Our study indicated that the short-term outcomes for patients with vascular resection were poor, compared with those not undergoing vascular resection. The long-term survival of patients following vascular invasion was more favorable in R0M0 disease, although neither PVI nor HAI was associated with significant differences in OS in the multivariate analysis.

Insufficient numbers of reports incorporating multivariate analyses have been published to determine a relationship between vascular resection and postoperative mortality following PHC surgery.[7, 16] Similarly, reports on the significance of vascular invasion[17, 18] (hepatic artery[19] or PV[9, 10, 20]) on surgical outcomes are also lacking. Therefore, this study examined these issues.

Among recent reports describing > 20 PVRs for PHC, excluding ones at the same facility, some suggest that PVR does not influence surgical mortality,[3, 4, 16, 21, 22] but a few indicate that it does.[7, 23] Even in some systematic reviews, different results have been reported regarding whether PVR does not[24–26] or does[27, 28] affect mortality. In addition, PV thrombus, one of the important complications after PVR, has been reported to occur in 0–9.5% of cases.[4, 8, 17, 29–33] In the current study, hospital deaths were not due to problems arising in the reconstructed PV portion, despite five patients (7.2%) developing PV thrombus after PVR. Based on techniques associated with liver transplant surgery, 6-0 Prolene sutures have been used to prevent PV thrombus formation since 2016, although such thrombus formation seems to be common in high-volume centers. PVR seems to be a relatively safe procedure in facilities with surgeons having adequate experience[3, 4, 17, 21, 30]; however, more attention is necessary to prevent postoperative vascular complications.

In recent studies that have included > 20 HARs associated with PHC surgeries, excluding those occurring at the same facility, the associated mortality rate is 2.0–9.1%.[1, 2, 17, 34–36] Some of the available reports, including systematic reviews, indicate that HAR does not seem to be related to surgical mortality,[2, 16, 35] but others suggest that it is.[24, 28] Nagino et al., in their largest case series,[1] and others[2, 6, 17] state that major hepatectomies involving HAR and PVR can be performed by experienced surgeons and yield acceptable mortality rates. Facilities where many HARs have been performed also seem to have fewer vascular complications and reduced mortality.[1, 36] The mortality rate associated with HAR, in our series, was 15.7% (3/19), which was higher than in those reports.[1, 2, 17, 34–36] Our series included two patients who underwent reconstructions performed by a general surgeon, and the obstructions occurred in the reconstructed section. It is inferred that this surgeon may have had insufficient experience with microscopic surgery. Following those deaths, HARs were performed exclusively by plastic surgeons. After excluding the HARs performed by the general surgeon, the mortality rate for HARs performed by plastic surgeons, in our series, was 5.9% (1/17); this result is similar to the results reported by other authors.[1, 2, 17, 34–36]

The authors believe that vascular resection is contraindicated in cases where R0 resection cannot be contemplated for vascular invasion, cases in which adequate vessel length cannot be secured for vascular reconstructions in future remnant livers, and in cases where reconstruction is difficult even using vascular grafts for extensive resections.

In previous reports, the factors predictive of survival associated with PHC surgery include microscopic vascular invasion, R0 resection,[4, 10] lymph node metastasis,[4, 6, 10, 17] histology,[4] T stage ≥ 3,[6] and adjuvant chemotherapy.[17] Both PVI and HAI were excluded as prognostic factors in some studies[9, 10, 17, 18] but not in all.[19, 20] The present study showed that both PVI and HAI had similar impacts on OS.

There are several reports indicating that the 5-year survival rate after PVR for PHC is 22.8–59%.[3, 4, 9, 21, 30, 37–40] In these reports, the post-PVR survival rate was reported to be inferior to that for patients not undergoing PVR but better than for cases that are unresectable[22, 30]; in other reports, no differences were observed in the survival rates of PVR and non-PVR cases.[3, 4, 10, 34] Regarding PVI, Nakanishi et al. reported a 5-year OS of 11.2% in patients with main or contralateral branch invasion, which was significantly worse than the 43% for patients with ipsilateral branch PV.[20] The median survival time for patients with vascular invasion (including HAI) was reported to be 8.9–38 months.[8, 9, 23, 41] Our results also show that the 5-year OS of PVIM0R0 patients was significantly worse than for aPVIM0R0 patients but significantly better than for PVIM1 or R1 patients (Fig. 2); the 5-year OS was not significant in PVIM0R0/1cis patients, with or without PVR (Supplemental Fig. 1).

Regarding HAI, Nagino et al. reported a 5-year survival rate of 22.6% for 50 consecutive cases of patients with HAI undergoing HAR ($n = 27$).[1] Matsuyama et al. reported that the 5-year survival rate and median survival time for patients with HAI and undergoing HAR ($n = 20$) were 0% and 38.1 months.[17] In the current study, the 5-year OS for HAIM0R0/1cis patients was significantly worse than that for

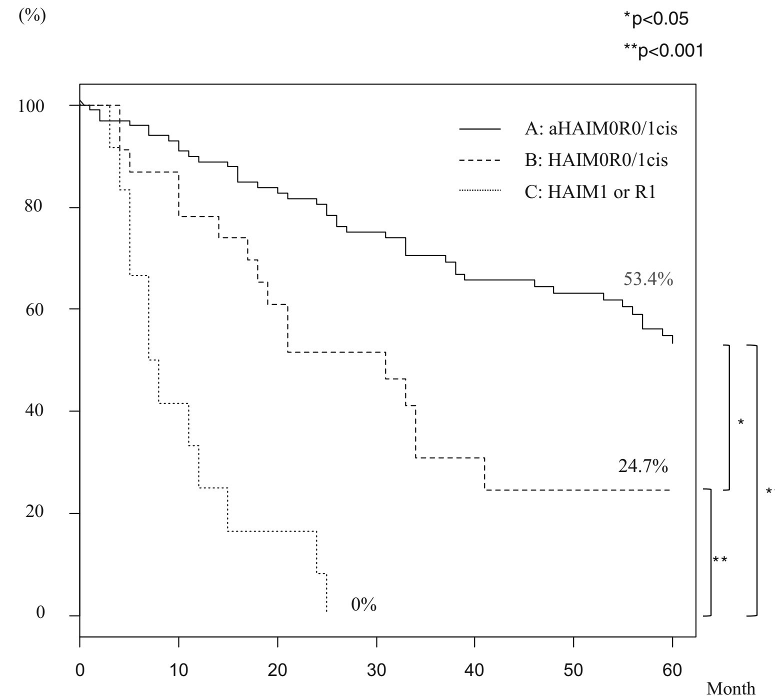


Fig. 2 Overall survival rates, based on the presence or absence of histopathological hepatic artery invasion (HAI, aHAI) in patients with distant metastasis-negative (M0) tumors, with negative or high-grade dysplasia/carcinoma in situ surgical margins (R0/1cis), distant metastasis-positive (M1), or bile duct stump-positive cases with invasive cancer (R1). The median survival time was not determined for aHAIM0R0/1cis patients but was 31 months in HAIM0R0/1cis patients and 7.5 months in HAIM1 or R1 patients. *$p < 0.05$, **$p < 0.001$. HAI, presence of histopathological hepatic artery invasion; aHAI, absence of histopathological hepatic artery invasion; M1, distant metastasis; R0, negative surgical margin; R1cis, high-grade dysplasia/carcinoma in situ of the bile duct margin; R1, bile duct stump-positive cases with invasive cancer, with or without any other residual cancer; NS, not significant

Tumor type	Number at risk	2 years	5 years
aHAIM0R0/cis	99	76	38
HAIM0R0/1cis	23	11	3
HAIM1 or R1	12	2	0

patients with aHAIM0R0/1cis but better than for those with HAIM1 or R1. However, the 5-year OS in patients with HAI and HAR ($n = 8$) was 0%. The reason for the absence of long-term survivors of this type, in our series, is probably the few patients with HAI who underwent HAR ($n = 8$); all of our patients had at least one negative prognostic factor, such as lymph node metastases ($n = 5$), invasive R1 disease ($n = 3$), high preoperative carcinoembryonic antigen levels ($n = 1$), or postoperative peritoneal dissemination by percutaneous transhepatic biliary drainage ($n = 1$).

Limitations

This study has some limitations. This was a single-institution, retrospective study, and involved patient data collected over 15 years. During this period, patient management protocols, such as diagnostic modalities, perioperative management procedures, biliary drainage use, surgical indications, and surgical device use, changed drastically.

Conclusions

Vascular resection for PHC can be performed relatively safely in specialized facilities. However, our data indicate that short-term outcomes in cases involving vascular resection were poor compared with those not involving vascular resection. The long-term survival of patients with vascular invasion was more favorable for patients with R0M0 disease. Aggressive surgery should be performed, where possible, in selected patients.

Acknowledgments The authors thank Kenichiro Imai, Hideki Kajiyama, and Mimi Okano, Department of Surgery, Tokyo Women's Medical University, for surgical assistance and Editage (www.editage.jp) for English language editing.

Author Contributions Conception and design of the study: RH. Acquisition of data: RH, TY, SU, WI, OT, TF, HE, and MY. Analysis and interpretation of data: RH. Pathological diagnosis: TF. Draft and critical analysis: RH and MY.

References

1. Nagino M, Nimura Y, Nishio H, Ebata T, Igami T, Matsushita M, Nishikimi N, Kamei Y. Hepatectomy with simultaneous resection of the portal vein and hepatic artery for advanced perihilar cholangiocarcinoma: an audit of 50 consecutive cases. Ann Surg 2010;252:115–123.
2. Noji T, Tsuchikawa T, Okamura K, Tanaka K, Nakanishi Y, Asano T, Nakamura T, Shichinohe T, Hirano S. Concomitant hepatic artery resection for advanced perihilar cholangiocarcinoma: a case-control

study with propensity score matching. J Hepatobiliary Pancreat Sci 2016;23:442–448.
3. Hemming AW, Mekeel K, Khanna A, Baquerizo A, Kim RD. Portal vein resection in management of hilar cholangiocarcinoma. J Am Coll Surg 2011;212:604–613.
4. Lee SG, Song GW, Hwang S, Ha TY, Moon DB, Jung DH, Kim KH, Ahn CS, Kim MH, Lee SK, Sung KB, Ko GY. Surgical treatment of hilar cholangiocarcinoma in the new era: the Asan experience. J Hepatobiliary Pancreat Sci 2010;17:476–489.
5. Miyazaki M, Yoshitomi H, Miyakawa S, Uesaka K, Unno M, Endo I, Ota T, Ohtsuka M, Kinoshita H, Shimada K, Shimizu H, Tabata M, Chijiiwa K, Nagino M, Hirano S, Wakai T, Wada K, Isayama H, Okusaka T, Tsuyuguchi T, Fujita N, Furuse J, Yamao K, Murakami K, Yamazaki H, Kijima H, Nakanuma Y, Yoshida M, Takayashiki T, Takada T. Clinical practice guidelines for the management of biliary tract cancers 2015: the 2nd English edition. J Hepatobiliary Pancreat Sci 2015;22:249–273.
6. Schimizzi GV, Jin LX, Davidson JTt, Krasnick BA, Ethun CG, Pawlik TM, Poultsides G, Tran T, Idrees K, Isom CA, Weber SM, Salem A, Hawkins WG, Strasberg SM, Doyle MB, Chapman WC, Martin RCG, Scoggins C, Shen P, Mogal HD, Schmidt C, Beal E, Hatzaras I, Shenoy R, Maithel SK, Fields RC. Outcomes after vascular resection during curative-intent resection for hilar cholangiocarcinoma: a multi-institution study from the US extrahepatic biliary malignancy consortium. HPB (Oxford) 2018;20:332–339.
7. Shen P, Fino N, Levine EA, Eversole P, Clark C. Bile duct surgery in the treatment of hepatobiliary and gallbladder malignancies: effects of hepatic and vascular resection on outcomes. HPB (Oxford) 2015;17:1066–1073.
8. Hoffmann K, Luible S, Goeppert B, Weiss KH, Hinz U, Büchler MW, Schemmer P. Impact of portal vein resection on oncologic long-term outcome in patients with hilar cholangiocarcinoma. Surgery 2015;158:1252–1260.
9. Neuhaus P, Thelen A, Jonas S, Puhl G, Denecke T, Veltzke-Schlieker W, Seehofer D. Oncological superiority of hilar en bloc resection for the treatment of hilar cholangiocarcinoma. Ann Surg Oncol 2012;19:1602–1608.
10. de Jong MC, Marques H, Clary BM, Bauer TW, Marsh JW, Ribero D, Majno P, Hatzaras I, Walters DM, Barbas AS, Mega R, Schulick RD, Choti MA, Geller DA, Barroso E, Mentha G, Capussotti L, Pawlik TM. The impact of portal vein resection on outcomes for hilar chol:angiocarcinoma: a multi-institutional analysis of 305 cases. Cancer 2012;118:4737–4747.
11. Higuchi R, Yazawa T, Uemura S, Yamamoto M. Anterior approach for perihilar cholangiocarcinoma (with video). J Surg Res 2016;202:71–76.
12. Higuchi R, Ota T, Yazawa T, Kajiyama H, Araida T, Furukawa T, Yoshikawa T, Takasaki K, Yamamoto M. Improved surgical outcomes for hilar cholangiocarcinoma: changes in surgical procedures and related outcomes based on 40 years of experience at a single institution. Surg Today 2016;46:74–83.
13. Ebata T, Kamiya J, Nishio H, Nagasaka T, Nimura Y, Nagino M. The concept of perihilar cholangiocarcinoma is valid. Br J Surg 2009;96:926–934.
14. Nagorney DM, Pawlik TM, Chun YS, Vauthey JN. AJCC Cancer staging manual: Springer, 2017:311–316.
15. Miyazaki M, Ohtsuka M, Miyakawa S, Nagino M, Yamamoto M, Kokudo N, Sano K, Endo I, Unno M, Chijiiwa K, Horiguchi A, Kinoshita H, Oka M, Kubota K, Sugiyama M, Uemoto S, Shimada M, Suzuki Y, Inui K, Tazuma S, Furuse J, Yanagisawa A, Nakanuma Y, Kijima H, Takada T. Classification of biliary tract cancers established by the Japanese Society of Hepato-Biliary-Pancreatic Surgery: 3(rd) English edition. J Hepatobiliary Pancreat Sci 2015;22:181–196.
16. Nagino M, Ebata T, Yokoyama Y, Igami T, Sugawara G, Takahashi Y, Nimura Y. Evolution of surgical treatment for perihilar cholangiocarcinoma: a single-center 34-year review of 574 consecutive resections. Ann Surg 2013;258:129–140.
17. Matsuyama R, Mori R, Ota Y, Homma Y, Kumamoto T, Takeda K, Morioka D, Maegawa J, Endo I. Significance of vascular resection and reconstruction in surgery for hilar cholangiocarcinoma: with special reference to hepatic arterial resection and reconstruction. Ann Surg Oncol 2016;23:475–484.
18. Konstadoulakis MM, Roayaie S, Gomatos IP, Labow D, Fiel MI, Miller CM, Schwartz ME. Aggressive surgical resection for hilar cholangiocarcinoma: is it justified? Audit of a single center's experience. Am J Surg 2008;196:160–169.
19. Chen KJ, Yang FC, Qin YS, Jin J, Zheng SS. Assessment of clinical outcomes of advanced hilar cholangiocarcinoma. Hepatobiliary Pancreat Dis Int 2018;17:155–162.
20. Nakanishi Y, Tsuchikawa T, Okamura K, Nakamura T, Tamoto E, Murakami S, Ebihara Y, Kurashima Y, Noji T, Asano T, Shichinohe T. Prognostic impact of the site of portal vein invasion in patients with surgically resected perihilar cholangiocarcinoma. Surgery 2016;159:1511–1519.
21. Tamoto E, Hirano S, Tsuchikawa T, Tanaka E, Miyamoto M, Matsumoto J, Kato K, Shichinohe T. Portal vein resection using the no-touch technique with a hepatectomy for hilar cholangiocarcinoma. HPB (Oxford) 2014;16:56–61.
22. Miyazaki M, Kato A, Ito H, Kimura F, Shimizu H, Ohtsuka M, Yoshidome H, Yoshitomi H, Furukawa K, Nozawa S. Combined vascular resection in operative resection for hilar cholangiocarcinoma: does it work or not? Surgery 2007;141:581–588.
23. Young AL, Prasad KR, Toogood GJ, Lodge JP. Surgical treatment of hilar cholangiocarcinoma in a new era: comparison among leading Eastern and Western centers, Leeds. J Hepatobiliary Pancreat Sci 2010;17:497–504.
24. Abbas S, Sandroussi C. Systematic review and meta-analysis of the role of vascular resection in the treatment of hilar cholangiocarcinoma. HPB (Oxford) 2013;15:492–503.
25. Chen W, Ke K, Chen YL. Combined portal vein resection in the treatment of hilar cholangiocarcinoma: a systematic review and meta-analysis. Eur J Surg Oncol 2014;40:489–495.
26. Wu XS, Dong P, Gu J, Li ML, Wu WG, Lu JH, Mu JS, Ding QC, Zhang L, Ding Q, Weng H, Liu YB. Combined portal vein resection for hilar cholangiocarcinoma: a meta-analysis of comparative studies. J Gastrointest Surg 2013;17:1107–1115.
27. Bai T, Chen J, Xie ZB, Ma L, Liu JJ, Zhu SL, Wu FX, Li LQ. Combined portal vein resection for hilar cholangiocarcinoma. Int J Clin Exp Med 2015;8:21044–21,052.
28. Yu W, Gu Z, Shi S, Shen N, Zhang Y. Effect evaluation of vascular resection for patients with hilar cholangiocarcinoma: original data and meta-analysis. Cell Biochem Biophys 2014;69:509–516.
29. Young AL, Igami T, Senda Y, Adair R, Farid S, Toogood GJ, Prasad KR, Lodge JP. Evolution of the surgical management of perihilar cholangiocarcinoma in a Western centre demonstrates improved survival with endoscopic biliary drainage and reduced use of blood transfusion. HPB (Oxford) 2011;13:483–493.
30. Igami T, Nishio H, Ebata T, Yokoyama Y, Sugawara G, Nimura Y, Nagino M. Surgical treatment of hilar cholangiocarcinoma in the “new era”: the Nagoya University experience. J Hepatobiliary Pancreat Sci 2010;17:449–454.
31. Dumitrascu T, Stroescu C, Brasoveanu V, Herlea V, Ionescu M, Popescu I. Curative-intent surgery for perihilar cholangiocarcinoma with and without portal vein resection—a comparative analysis of early and late outcomes. Chirurgia (Bucur) 2017;112:308–319.
32. Song SC, Choi DW, Kow AW, Choi SH, Heo JS, Kim WS, Kim MJ. Surgical outcomes of 230 resected hilar cholangiocarcinoma in a single centre. ANZ J Surg 2013;83:268–274.
33. Shimizu H, Kimura F, Yoshidome H, Ohtsuka M, Kato A, Yoshitomi H, Furukawa K, Miyazaki M. Aggressive surgical resection for hilar cholangiocarcinoma of the left-side predominance:

radicality and safety of left-sided hepatectomy. Ann Surg 2010;251:281–286.
34. Wang ST, Shen SL, Peng BG, Hua YP, Chen B, Kuang M, Li SQ, He Q, Liang LJ. Combined vascular resection and analysis of prognostic factors for hilar cholangiocarcinoma. Hepatobiliary Pancreat Dis Int 2015;14:626–632.
35. Peng C, Li C, Wen T, Yan L, Li B. Left hepatectomy combined with hepatic artery resection for hilar cholangiocarcinoma: a retrospective cohort study. Int J Surg 2016;32:167–173.
36. Hu HJ, Jin YW, Zhou RX, Shrestha A, Ma WJ, Yang Q, Wang JK, Liu F, Cheng NS, Li FY. Hepatic artery resection for Bismuth type III and IV hilar cholangiocarcinoma: is reconstruction always required? J Gastrointest Surg 2018;22:1204–1212.
37. Reames BN, Ejaz A, Koerkamp BG, Alexandrescu S, Marques HP, Aldrighetti L, Maithel SK, Pulitano C, Bauer TW, Shen F, Poultsides GA, Martel G, Marsh JW, Pawlik TM. Impact of major vascular resection on outcomes and survival in patients with intrahepatic cholangiocarcinoma: a multi-institutional analysis. J Surg Oncol 2017;116:133–139.
38. Endo I, Matsuyama R, Mori R, Taniguchi K, Kumamoto T, Takeda K, Tanaka K, Köhn A, Schenk A. Imaging and surgical planning for perihilar cholangiocarcinoma. J Hepatobiliary Pancreat Sci 2014;21:525–532.
39. Chang J, Jang JY, Kang MJ, Jung W, Shin YC, Kim SW. Clinicopathologic differences in patients with gallbladder cancer according to the presence of anomalous biliopancreatic junction. World J Surg 2016;40:1211–1217.
40. Song GW, Lee SG, Hwang S, Kim KH, Cho YP, Ahn CS, Moon DB, Ha TY. Does portal vein resection with hepatectomy improve survival in locally advanced hilar cholangiocarcinoma? Hepatogastroenterology 2009;56:935–942.
41. Hidalgo E, Asthana S, Nishio H, Wyatt J, Toogood GJ, Prasad KR, Lodge JP. Surgery for hilar cholangiocarcinoma: the Leeds experience. Eur J Surg Oncol 2008;34:787–794.