Int J Clin Exp Med 2017;10(2):2695-2705
www.ijcem.com /ISSN:1940-5901/IJCEM0040333

Original Article

Combined vascular resection and reconstruction for advanced hilar cholangiocarcinoma

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Received September 20, 2016; Accepted November 22, 2016; Epub February 15, 2017; Published February 28, 2017

Abstract: Background: Hilar cholangiocarcinoma with vascular invasion was previously regarded as locally advanced disease and a contraindication to curative resection. The significance of combined vascular resection and reconstruction has remained ambiguous and controversial. This study aimed to reveal the role and efficacy of concomitant vascular resection and reconstruction on survival of patients with hilar cholangiocarcinoma. Materials and Methods: From January 2006 to December 2014, totally 19 out of 95 hilar cholangiocarcinoma patients undergoing curative resection were performed with combined vascular resection and reconstruction in a single institute including right hepatic artery alone (n=6), portal vein plus right hepatic artery (n=3) and portal vein alone (n=10), the remaining 67 patients underwent without vascular resection. The clinicopathologic features and survival outcomes of candidates were analyzed retrospectively. Results: The one, three and five-years survival rates in vascular reconstruction group were 78.8%, 21.3%, 0% respectively, comparing with that of non-vascular resection group 79.3%, 31.8%, 12.3% respectively (*P*=0.416). Median survival time in vascular reconstruction group was 17 months with mortality of 5.26% (1/19), which was close to that of non-vascular resection group. Pathological examination confirmed 36.84% patients (7/19) were with microscopic invasion. Multivariate analysis showed that CA-199 above 200 U/ml (*P*=0.035) and pathological differentiation (*P*=0.015) were independent prognostic factors of adverse effect on postoperative survival. Conclusion: Combined vascular resection and reconstruction for advanced hilar cholangiocarcinoma could improve survival with acceptable efficacy and safety in selected patients.

Keywords: Hilar cholangiocarcinoma, vascular resection, hepatic artery resection, portal vein resection, survival

Introduction

Hilar cholangiocarcinoma (HCCA) with the propensity of extensiveness infiltration usually invades adjacent to major hilar vasculatures including portal vein, hepatic artery [1, 2]. Moreover, vascular invasion was previously regarded as locally advanced disease and a contraindication of curative resection due to the fact that it was hard to achieve negative margin [3]. However, currently, curative resection but no alternative treatment has been the only potential curable approach for HCCA and no alternative therapies has offered survival comparable with surgical resection [4, 5]. With the advance of surgical strategies and surgical techniques, inspiring survival outcomes for advanced HCCA patients has come to be possible after simultaneously with vascular resection and reconstruction [6-9]. We have also performed combined vascular resection and reconstruction for advanced HCCA patients in the recent decade. This retrospective study was undertaken to elucidate whether combined vascular resection and reconstruction for HCCA was beneficial and evaluate the safety and efficacy of this procedure for selected advanced HCCA patients.

Materials and methods

Patients

This study was approved by the local institutional review board of Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University. The data of this study was extracted from patients medical records and a prospectively collected database

Table 1. Clinicopathologic and demographic features of 95 HCCA patients who underwent curative resection

	Vascular resection group	Non-vascular resection group	*P*-value
Number of patients	n=19	n=76	
Age (years)	55.40±11.88	61.03±10.48	0.045
Gender	M=14, F=5	M=43, F=33	0.173
Serum total bililubin (umol/L)	242.8±137.14	213.11±143.95	0.420
CEA (ng/ml)	4.33±3.46	7.5±23.89	0.794
CA199 (U/ml)	7753.6±22914.28	1031.96±2081.51	0.103
ALB (g/L)	36.77±5.43	38.25±4.71	0.198
Hepatitis infection	3	9	0.701
Bismuth Corlette classification			0.691
I/II	2	15	
IIIA	2	7	
IIIB	8	23	
IV	7	31	
PTCD	8	18	0.107
Pathological differentiation			0.813
Well	6	27	
Moderate	8	26	
Poor	5	23	
Perineural invasions	11	40	0.681
Lymph nodes invasion	16	31	0.001
Microscopic vascular invasion	7	12	0.057

established by the department of Hepatobiliary, Memorial Hospital, Sun Yat-Sen University. Between January 2006 and December 2014, a total of 142 HCCA patients underwent surgical resection, and R0 resection confirmed pathologically was achieved in 95 patients that were the subjects of this study. Based on whether concomitant vascular reconstruction was performed, 95 patients were stratified into two groups: vascular reconstruction group (n=19), non-vascular resection group (n=76). The vessels involved in vascular reconstruction group were as followed: right hepatic artery alone (n=6), portal vein plus right hepatic artery (n=3) and portal vein alone (n=10). The details of clinicopathologic and demographic features of enrolled patients were depicted in **Table 1**.

Preoperative assessment

To establish the nature, assess extent of tumor and identify vasculatures details as well as estimate remnant liver volume, laboratory examination and imaging workups of ultrasonography, magnetic resonance cholangiopancreatography (MRCP), multi-detector row computed tomography (MDCT) were performed for all candidates. Additionally, patients who were scheduled to accept major hepatectomy with serum total bilirubin over 200 umol/L were suggested with preoperative biliary drainage prior to surgery. 26 out of 95 candidates underwent preoperative biliary drainage via percutaneous transhepatic cholangial drainage (PTCD) or endoscopic nasal biliary drainages (ENBD) including 8 patients of vascular reconstruction group (PTCD=7, ENBD=1). In addition, no preoperative portal vein embolization (PVE) was indicated in any patients. Ultimately, general condition of all candidates met the requirements of Child-Pugh classification (grade A to B), which to certain extent warrants the safety of surgery.

Operative procedures

Surgical procedures consisting of hemihepatectomy, extended hemihepatectomy, central hepatectomy, external bile duct resection with or without caudate lobectomy as well as combined invaded vessels resection and reconstruction were performed for patients individu-

Table 2. Surgical procedures of 19 HCCA patients with vascular reconstruction

Details of vascular resection and reconstruction	Number of patients
Bismuth Corlette classification	19
I	0
II	2
IIIA	2
IIIB	8
IV	7
Preoperative drainage	8
PTCD	7
ENBD	1
Surgical procedure	
Left hepatectomy	14
With S1 lobectomy	8
Without S1 lobectomy	6
Extended left hepatecomy	3
With S1 lobectomy	2
Without S1 lobectomy	1
Right hepatectomy	1
With S1 lobectomy	0
Without S1 lobectomy	1
Extended right hepatectomy	1
Types of vessels invasion and reconstruction modes	
Portal vein bifurcation only	10
End to end (E to E)	9
Vascular graft	1
Right hepatic artery only	6
End to end	5
Anastomosis with gastrointestial artery	1
Portal vein plus hepatic artery	3
Portal vein bifurcation (E to E) plus right hepatic artery (E to E)	2
Portal vein bifurcation (E to E) plus hepatic proper artery (anastomosis gastrointestinal artery with right hepatic artery)	1
Portal vein bifurcation only	10
End to end (E to E)	9

ally. Locoregional lymph nodes including nodes along the common hepatic artery, in the hepatoduodenal ligament, and posterior pancreaticoduodenal nodes were routinely dissected for all patients, and aggressive lymph nodes dissection was decided by the attending surgeons. Upon completion of tumor resection, biliary continuity was restored by Roux-en-Y anastomosis. To further analyze the nature of tumor affecting the prognosis, tumor was classified as well differentiated, moderately differentiated, poorly differentiated adenocarcinoma after resection according to the predominant pathologic grading of differentiation. Besides that, perineural invasions, lymph nodal metastases and microscopic vascular invasion that generated from pathological results were also further assessed.

Approach to vascular resection and reconstruction

Preoperative MDCT or MRCP was routinely applied to assess infiltration of vessels. Surgical policies of portal vein or hepatic artery resection and reconstruction were carried out only when vessels adhered to and could not be freed from tumor entity during intraoperative skeletonization of hepatoduodenal ligament [10]. The portal vein was reconstructed by model of end to end anastomosis (n=12) or vascular grafts (n=1) between the resected residual trunk and corresponding branch, and the hepatic artery reconstruction relied on end to end fashion (n=4) or anastomosis with gastroduodenal artery (n=2). None of patients in vascular reconstruction group was performed with portal vein arterialization (PVA). Vascular patency after surgery was assessed by Doppler ultrasonography or MDCT. The details of surgical procedures for vascular resection and reconstruction were depicted in **Table 2**. A typical portal vein reconstruction with vascular graft was presented in **Figures 1** and **2**.

Morbidity and mortality

Mortality was defined as any postoperative death occurring in-hospital stay. Major compli-

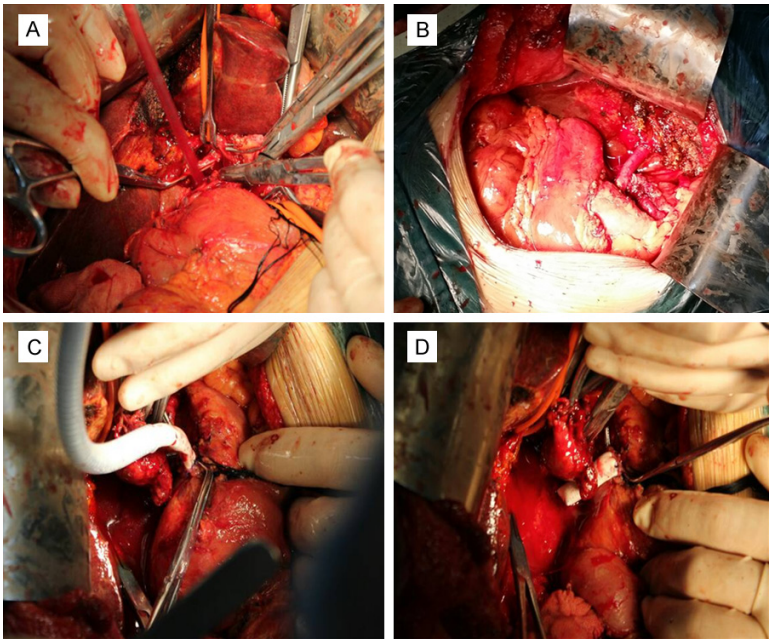

Figure 1. Portal vein resection and reconstruction with vascular graft. A: Ready for resection; B: Removed the tumor mass with left hepatectomy; C: Vascular graft anastomosis with distal portal vein; D: Vascular graft anastomosis with proximal portal vein.

cations were regarded as having a grade of III-IV complication according to the Clavien-Dindo Classification [11].

Statistics

Continuous variables were expressed as mean ± standard deviation. Categorical variables were expressed as numbers. Continuous or categorical variables comparison between these two groups was performed by a Student's t test (two-tailed) or Mann-Whitney U tests and χ^2 test or Fisher's exact test. Cumulative Survival time counted from the month of surgery was calculated with the Kaplan-Meier method and difference in survival curves were compared with log-rank test, respectively. The Cox proportional hazard model was used for multivariate analysis of survival after curative resection basing on the interesting variables that were statistically significant by univariate analysis. A *P*-value <0.05 was considered as statistically significance. Statistical analysis was performed with SPSS software, version 17.0.

Results

Clinicopathologic and demographic features

The current study population consisted of 57 male and 38 female patients with a mean age of 59.9 years (range, 28-82 years). According to the Bismuth-Corlette Classification, 9 patients were with type I, 8 with type II, 9 with type IIIA, 31 with type IIIB, 38 with type IV. The clinicopathologic and demographic features showed no significant difference factors between two groups in **Table 1**, except for age, lymph node invasion.

Operation data

The mean operation time for patients in vascular reconstruction group was 6.26± 1.08 h. The mean amount of blood loss was 563.16±377.4 ml and blood transfusion was performed on 5 patients during operation with mean 3 U red blood cell transfusion. The median time for portal vein reconstruction was 10.8 minutes and that of hepatic artery reconstruction was 9.4 minutes. Vascular anastomosis was constructed by continuous sutures with 7-0/8-0 prolene.

Morbidity and mortality

Postoperative complications occurred to 84.2% patients (n=16) of 19 patients including 6 with major complication. Bile leakage was the most common complication (n=10, 52.6%), following the ascites (n=3, 15.8%) and intra-abdominal infection (n=3, 15.8%). One patient (5.26%) encountered a second laparotomy due to intra-abdominal bleeding within 7 days after surgery and one patient (5.26%) who underwent portal vein reconstruction died of liver failure resulting in multiple organ failure within 2 weeks postoperatively. Neither arterial aneurysm nor vascular thrombi nor vascular occlusion nor vascular anastomosis bleeding was identified in patients of vascular reconstruction group. The more details of morbidity and mortality of each group was summarized in **Table 3**.

Survival

The 1-year, 3-year and 5-year survival rate were 78.8%, 21.3%, 0%, respectively in vascular reconstruction group with median survival time

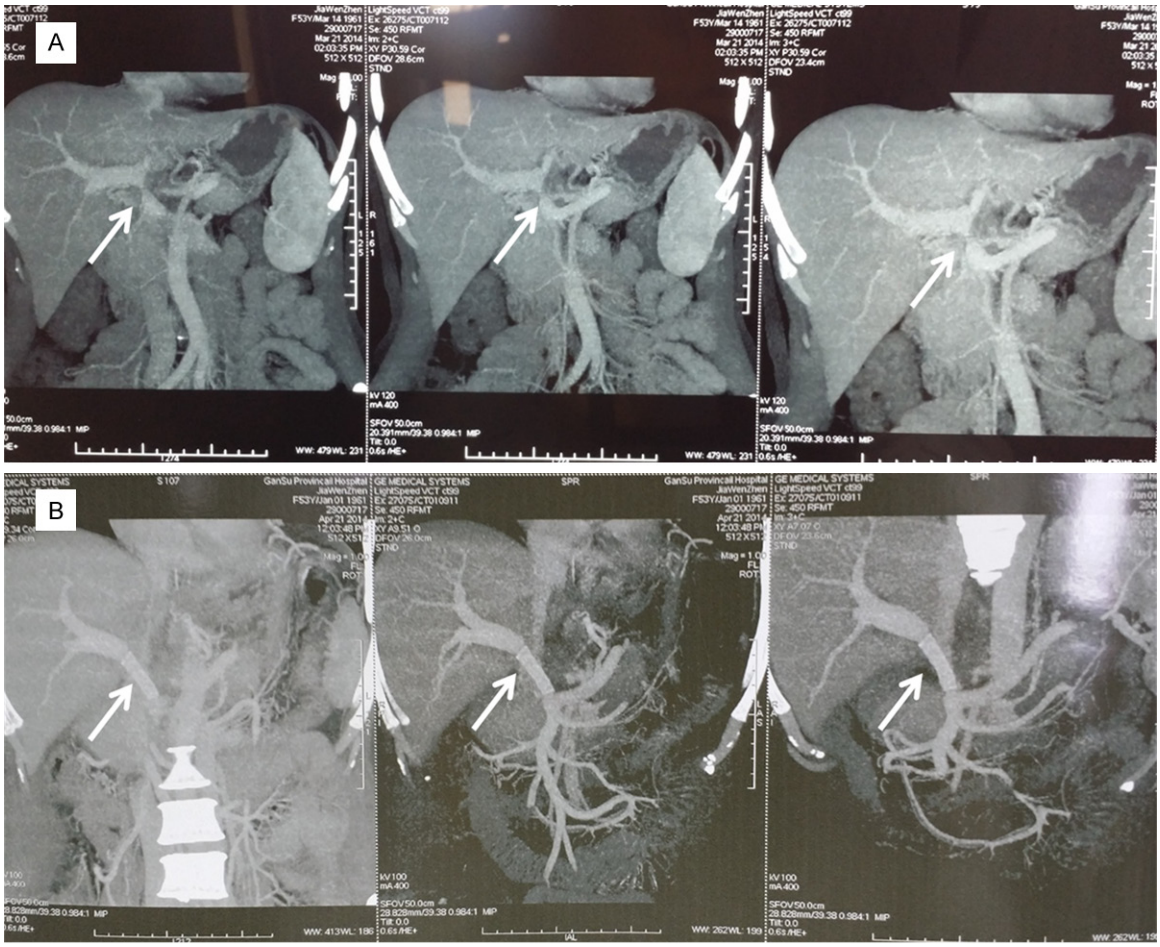

Figure 2. A advanced HCCA patient with portal vein invasion underwent combined portal vein resection and reconstruction with vascular graft. Preoperative MRI examination (A) showed the type IIIB lesion with contralateral portal vein invasion. One month later, postoperative MRI examination (B) presented that the invaded portal vein was resected and reconstructed vessel with vascular graft kept patent.

of 17 months and 79.3%, 31.8%, 12.3% respectively in non-vascular group with median survival time of 22 months (P=0.416, **Figure 3**). At the median follow up time of 32 months, there are still 6 patients alive in vascular reconstruction group. Moreover, 2 out of these 6 patients survived more than 30 months with tumor free and one of them underwent right hepatic artery plus portal vein reconstruction, the other one was after hepatic artery reconstruction alone.

Analysis of prognostic factors

In this series, univariate analysis based on Kaplan-Meier method showed that pathological differentiation, Lymph node invasion and CA-199 above 200 U/ml proved to be significant factors (**Figure 4**). Simultaneously, multivariate Cox proportional hazards regression analysis also identified that CA-199 above 200 U/ml (P=0.035) and pathological differentiation (P=0.015) were independent prognostic factors affecting postoperative survival (**Table 4**).

Discussion

Vascular invasion was a major obstacle to achieve radical resection for advanced HCCA previously. However, with the progress of advanced hepatobiliarypancreatic surgeries, concomitant vascular resection and reconstruction are currently recognized as a means to increase the rate of resectability with acceptable survival and mortality [12, 13]. The reported percentage of portal vein resection in HCCA varies from 9.8 to 37% and that from 1.7 to 18

Table 3. Complications of 95 HCCA patients with curative resection

	No. of patients in vascular reconstruction group n=19	No. of patients in non-vascular resection group n=76
Morbidity[a]		
Grade IVa		
Hepatic encephalopathy	0	1 (1.3%)
Hepatic or renal insufficiency	0	4 (5.3%)
ARDS	0	2 (2.6%)
Grade IIIb		
Intra-abdominal abscess	0	0
Liver abscess	0	0
Bilioenteric anastomosis bleeding	0	2 (2.6%)
Intra-abdominal bleeding	1 (5.2%)	2 (2.6%)
Grade IIIa		
Intra-abdominal abscess	0	2 (2.6%)
Gastrointestinal bleeding	1 (5.2%)	8 (10.5%)
Pleural effusion	1 (5.2%)	12 (15.8%)
Ascites	3 (15.8%)	17 (22.4%)
Liver absecess	0	1 (1.3%)
Grade II		
Bile leakage	10 (52.6%)	28 (36.8%)
Pneumonia	2 (10.4%)	13 (17.1%)
Pulmonary abscess	0	1 (1.3%)
Intra-abdominal infection	3 (15.8%)	18 (23.7%)
Sepsis	0	8 (10.5%)
Wound infection	1 (5.2%)	2 (2.6%)
Grade I	4 (21.0%)	10 (13.16%)
No. of complications	19	136
No. of Patients with complications	16 (84.21%)	45 (59.2%)
No. of Patients with major complications	6 (31.58%)	23 (30.26%)
Postoperative hospital stays (day)	19±16.4	16±25.7
Mortality		
In-hospital death	1 (5.2%)	3 (3.95%)

[a]: according to the Clavein-Dindo classification.

% [14-16] of hepatic artery resection. The 5-year survival rate of combined portal vein reconstruction for advanced HCCA from leading centers was close to 9.9%-25% with mortality of 16-17% [17-20], while few 5-year survivor with hepatic artery reconstruction was reported with higher mortality of 33-55% [1].

Nagigo et al [9] reported that the overall R0 resection rate was 66% with 1-, 3-, and 5-year survival rates of 78.9%, 36.3%, 30.3% respectively and mortality of 2% for 50 patients of advanced HCCA who underwent simultaneous portal vein and hepatic artery reconstruction. In the study of Miyazki et al [1], the 1-, 3-, 5-year survival rates in portal vein reconstruction group were 47%, 31%, and 25%, respectively and that of 17%, 0%, 0%, respectively in hepatic artery reconstruction group. Additionally, Gerhards et al [21] performed combined vascular resection for 12 HCCA patients including hepatic artery (n=2), portal vein (n=3) and portal vein plus hepatic artery (n=7), but the mortality of portal vein resection group was 3/10 and 5/9 of hepatic artery resection group. Based on the previous literatures published, it seemed to reveal that survival of combined hepatic artery resection was inferior to that in portal vein resection and may bring about higher mortality. The possible explanation for this discrepancy was that hepatic artery resection were required combined resection of affected portal vein in most patients, which may obligate longer periods of liver ischemia for vascular reconstruction and result in more severe ischemic damage to the remnant liver after major hepatectomy [1].

Additionally, right hepatic artery involvement is more frequent in HCCA patients due to its proximity to biliary bifurcation [1, 6, 7, 9, 13], which was main reason why most surgeons favor right hepatectomy for patients with type IV lesion. For one thing, preserving the right hepatic artery and right portal vein could be an oncological problem with left or extended left hepatectomy, which could cause tumor cell dissemination [22]. For another, the left hepatic artery runs through the leftmost portion of the hepatoduodenal ligament and can be left undisturbed during right-sided hepatectomy [6]. Furthermore, it is the fact that the right liver accounts for 60-70% of the total liver volume. Therefore, to certain extent, right hemihepatectomy or extended right hemihepatectomy carries more

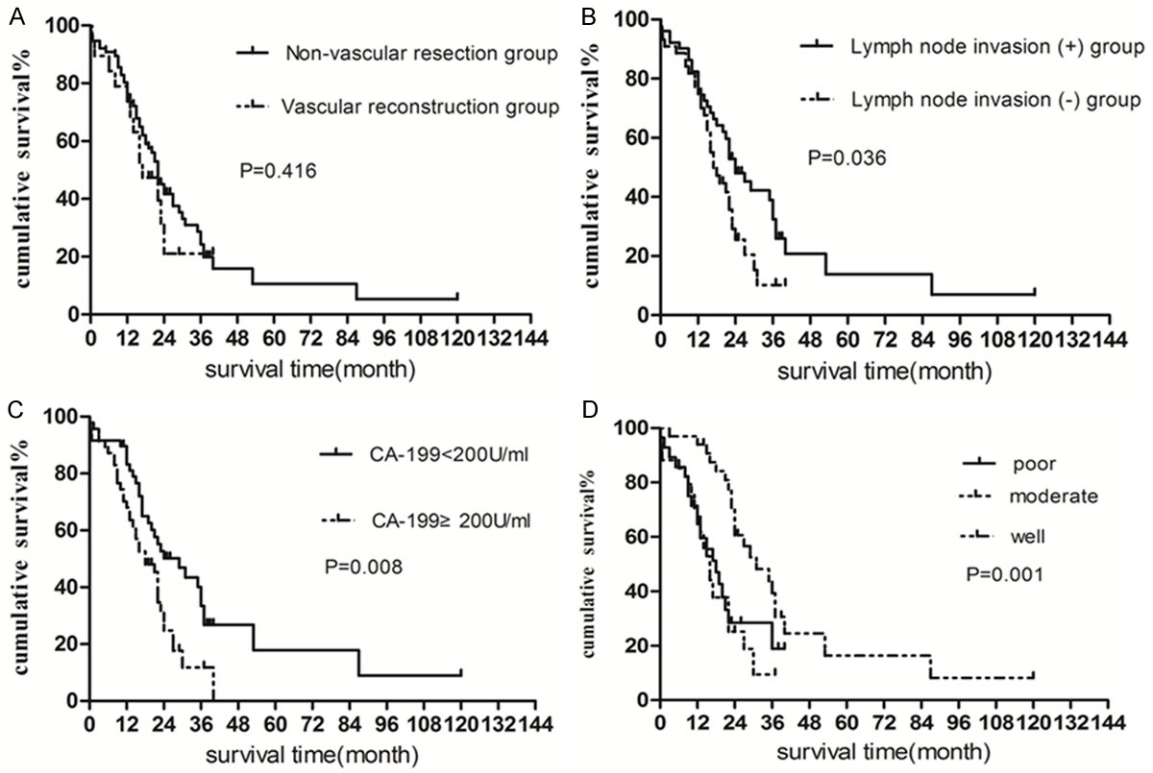

Figure 3. Cumulative Survival curves were calculated with Kaplan-Meier method. Survival of combined vascular resection and reconstruction group was comparable of that in non-vascular resection and reconstruction (*P*=0.416). Univariate analysis identified that lymph node invasion, preoperative CA-199≥200 U/ml, and pathologic differentiation were the significant factors affecting postoperative survival.

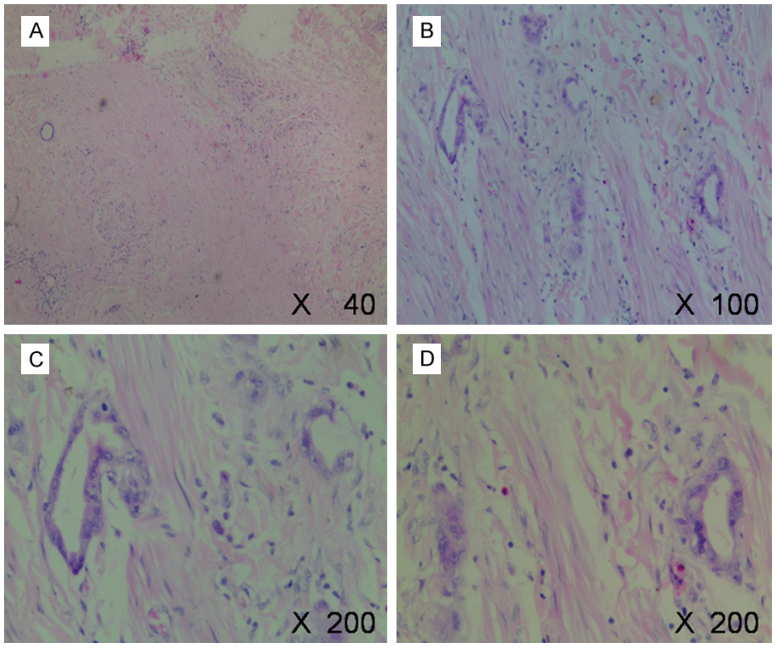

Figure 4. Microscopic invasion of resected portal vein was confirmed by pathologic examination under different microscopic magnification.

surgical risks on postoperative liver failure, even death. On the contrary, 9 patients of type IV lesion (47.37%) with right hepatic artery infiltration were performed with left hemihepatectomy and right hepatic artery reconstruction in this series. As a result, all these 9 patients obtained R0 resection and none of patients suffered from acute liver failure. From a surgeon's perspective, surgical policy was flexible that may largely depend on the predominance of tumor location, especially for type IV lesion with contralateral vascular invasion.

In the present study, 1-year and 3-year survival rates were 78.8%, 21.3% respectively as

Table 4. Univariate and Multivariate analysis of 95 HCCA patients with curative resection

Factors	No. of Patients	Univariate analysis			Multivariate analysis	
		Median survival (month)	x^2 value	*P*-value	RR (95% *CI*)	*P*-value
Age			1.701	0.192		
<60	47	22				
≥60	48	17				
Gender			0.264	0.608		
Male	57	23				
Female	38	21				
Preoperative TBIL			3.371	0.066		
<170 umol/l	54	24				
≥170 umol/L	41	16				
CEA level			0.003	0.955		
<15 ng/ml	93	22				
≥15 ng/ml	2	0.3				
CA-199 level			7.134	0.008		0.035
<200 U/ml	48	29			Reference	
≥200 U/ml	47	18			1.767, 95% CI (1.041-2.997)	
ALB level			0.049	0.824		
<35 g/L	16	22				
≥35 g/L	79	22				
Hepatitis infection			0.089	0.766		
Present	12	22				
Absent	83	22				
Bismuth Corlette Classification			5.338	0.254		
I	9	21				
II	8	16				
IIIA	9	14				
IIIB	31	22				
IV	38	23				
Preoperative PTCD			0.615	0.433		
Present	26	22				
Absent	69	22				
Combined hepatectomy			0.171	0.679		
Present	82	22				
Absent	13	22				
Caudate lobectomy			0.008	0.778		
Present	30	22				
Absent	65	20				
Vascular resection and reconstruction			0.663	0.416		
Present	19	17				
Absent	76	22				
Pathologic differentiation			13.755	0.001		0.015
Well	33	31			Reference	
Moderate	34	16			2.445, 95% CI (1.255-4.762)	
Poor	28	18			2.307, 95% CI (1.194-4.457)	
Lymph node invasion			4.38	0.036		0.629
Present	44	17			1.143, 95% CI (0.664-1.969)	
Absent	51	24			Reference	
Perineural invasions			0.002	0.888		
Present	48	22				
Absent	47	22				
Microscopic vascular invasion			0.536	0.464		
Present	19	17				
Absent	76	22				

well as the median survival time of 17 months in vascular reconstruction group, which was comparable of that in non-vascular resection (*P*=0.416). Although no patient in vascular reconstruction group has survived over 5 years till now, in comparison with median survival of 3 to 6 months of studies in terms of the natural history of advanced cholangiocarcinoma without any interventional procedures [23, 24], our results demonstrated significant survival improvement and benefits. Additionally, 2 patient who underwent concomitant portal vein and hepatic artery reconstruction have survived for 40 months, 20 months respectively with tumor free and another one has survived for 30 months after combined hepatic artery reconstruction. Although the outcomes of our study was not favorable but acceptable, at least, combined vascular resection and reconstruction have offered selected patients an opportunity for long-term survival.

Nevertheless, the incidence of histologically proven microscopic vascular invasion was lower in recent series than that of macroscopic vascular invasion [6, 9], a multivariate analysis of a convictive study [6] revealed that macroscopic invasion of portal vein but microscopic invasion had a negative impact on prognosis. Approximately one third of resected portal vein specimens were not infiltrated microscopically, yet tumor infiltration adjacent to portal vein was detected in most cases. Put another way, the resection margin would be positive without combined vascular resection. Undoubtedly, it has been an approved evidence to emphasize the necessities and effects of combined vascular resection for advanced HCCA. Similarly, in our series, pathologically microscopic vascular invasion was found in only 7 (36.8%) resected specimens in vascular reconstruction group (**Figure 4**). Multivariate analysis indicated that pathological differentiation was an independent prognostic factors for survival *(P*=0.015). Obviously, whatever the feature of macroscopic vascular invasion or pathological differentiation seems to be associated with biological behavior of HCCA. Therefore, further investigations are required to clarify the tumor nature that would cause far-reaching impact on survival for HCCA patients.

With no doubt, the toughest challenge for surgeons is how to identify vascular invasion and to rebuild vascular patency when those with severe tumor infiltration. Based on our limited experience and reviews, for one thing, both of invasion of Glission sheath and detecting local stenosis, distal pulses weaken or disappearance of hepatic artery intraoperatively may suggest vascular invasion. For another, vascular resection without detection preoperatively by MDCT or MRCP should be still recommended when vascular involvement was found on gross inspection during operation. With regard to vascular reconstruction, we tend to adopt vascular grafts or anastomosis with adjacent artery when suffering from the difficulty in hepatic artery reconstruction. In this series, 2 patients underwent anastomosis of right hepatic artery and gastroduodenal artery, and another one had vascular graft for portal vein reconstruction. Consequently, no liver failure occurred to each patient postoperatively. Additionally, PVA is also proposed to be a salvage therapy to maintain arterial inflow when hepatic artery reconstruction is impossible [25]. Because all of available reports were with small sample sizes, further investigations are required to measure its significance.

However, there were some drawbacks in this retrospective study. First and foremost, the survival and mortality of hepatic artery reconstruction was different from that of portal vein reconstruction, but they were combined into a new group due to small sample size, which may resulted in magnifying the survival benefits and reducing the morbidity rate as well as making statistically unreasonable. Furthermore, in light of the retrospective nature of most published series including the current one, more valid data about combined vascular resection and reconstruction should be provided by the future multi-center prospective studies. Last but not the least, owing to the randomization and control appearing hardly feasible, the actual benefits of combined vascular resection and reconstruction for advanced HCCA patients worth further exploring and clarifying.

In summary, combined vascular resection and reconstruction can be performed with acceptable prognosis and mortality for advanced HCCA patients.

Acknowledgements

This work was supported by Grant 15 y kpy 20 from the young stuff foundation of Sun Yat-Sen University; Grant [2013] 163 from Key Labo-

ratory of Malignant Tumor Mechanism and Translational Medicine of Guangzhou Bureau of Science and Information Technology; Grant KLB 09001 from the Key Laboratory of Malignant Tumor Gene Regulation and Target Therapy of Guangdong Higher Education Institutes.

Disclosure of conflict of interest

None.

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