ORIGINAL ARTICLE

Retrospective Cohort Study

Prognostic factors and long-term outcomes of hilar cholangiocarcinoma: A single-institution experience in China

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Abstract

AIM: To evaluate the prognostic factors of hilar cholangiocarcinoma in a large series of patients in a single institution.

METHODS: Eight hundred and fourteen patients with a diagnosis of hilar cholangiocarcinoma that were evaluated and treated between 1990 and 2014, of which 381 patients underwent curative surgery, were included in this study. Potential factors associated with overall survival (OS) and disease-free survival (DFS) were evaluated by univariate and multivariate analyses.

RESULTS: Curative surgery provided the best long-

term survival with a median OS of 26.3 mo. The median DFS was 18.1 mo. Multivariate analysis showed that patients with tumor size > 3 cm [hazard ratio (HR) = 1.482, 95%CI: 1.127-1.949; P = 0.005], positive nodal disease (HR = 1.701, 95%CI: 1.346-2.149; P < 0.001), poor differentiation (HR = 2.535, 95%CI: 1.839-3.493; P < 0.001), vascular invasion (HR = 1.542, 95%CI: 1.082-2.197; P = 0.017), and positive margins (HR = 1.798, 95%CI: 1.314-2.461; P < 0.001) had poor OS outcome. The independent factors for DFS were positive nodal disease (HR = 3.383, 95%CI: 2.633-4.348; P < 0.001), poor differentiation (HR = 2.774, 95%CI: 2.012-3.823; P < 0.001), vascular invasion (HR = 2.136, 95%CI: 1.658-3.236; P < 0.001), and positive margins (HR = 1.835, 95%CI: 1.256-2.679; P < 0.001). Multiple logistic regression analysis showed that caudate lobectomy [odds ratio (OR) = 9.771, 95%CI: 4.672-20.433; P < 0.001], tumor diameter (OR = 3.772, 95%CI: 1.914-7.434; P < 0.001), surgical procedures (OR = 10.236, 95%CI: 4.738-22.116; P < 0.001), American Joint Committee On Cancer T stage (OR = 2.010, 95%CI: 1.043-3.870; P = 0.037), and vascular invasion (OR = 2.278, 95%CI: 0.997-5.207; P = 0.051) were independently associated with tumor-free margin, and surgical procedures could indirectly affect survival outcome by influencing the tumor resection margin.

CONCLUSION: Tumor margin, tumor differentiation, vascular invasion, and lymph node status were independent factors for OS and DFS. Surgical procedures can indirectly affect survival outcome by influencing the tumor resection margin.

Key words: Hilar cholangiocarcinoma; Prognosis; Surgical outcome; Survival; Tumor-free margin

Core tip: Hilar cholangiocarcinoma remains among the most difficult management problems faced by surgeons. Although curative surgery prolongs the survival time of patients diagnosed with hilar cholangiocarcinoma, outcomes from studies may be contradictory or biased due to differences in study methods and small patient numbers. Furthermore, some large, multi-center reports may induce biases due to the heterogeneity of clinical methods and surgical strategies. Thus, we retrospectively analyzed the prognostic factors of hilar cholangiocarcinoma and factors associated with tumor-free margin in a large sample of hilar cholangiocarcinoma cases from a single institution.

INTRODUCTION

Hilar cholangiocarcinoma (HC) is a rare, devastating, and highly malignant disease of the bile duct[1-4]. On the basis of the Bismuth classification, hilar cholangiocarcinoma can be divided into four types: type Ⅰ represents tumors affecting the common hepatic duct, type Ⅱ represents tumors affecting the hilus, type Ⅲ A/B represents tumors invading the right or left hepatic duct, and type Ⅳ represents tumors infiltrating both right and left hepatic ducts and the subsegments[1]. A variety of risk factors are reported to increase the odds ratios of HCs, which include primary sclerosing cholangitis, biliary duct cysts, oriental cholangiohepatitis, hepatolithiasis, biliary parasitic disease, and toxins exposure, though the specific etiology is still unclear[5,6].

HC is reported to be a slow-growing and late-metastasizing malignant disease[7-9], but as it is situated at a cabinet and pivotal space, encircled by the portal vein, hepatic artery, liver parenchyma, and the bile duct, it has a strong tendency to extensively invade the portal vein, hepatic artery, perineural tissue, and surrounding liver parenchyma, including the caudate lobe[10-15]. Moreover, the caudate lobe lies in a deep and complex location and has an intimate relationship with the major vascular structures[16,17], resulting in high operative risks and increased postoperative complications[18,19]. In addition, HC always lies in the core part of the biliary system, causing malignant biliary obstruction and cholestatic hepatitis. Thus, major hepatic resection tends to be associated with increased risk of postoperative hepatic insufficiency, and postoperative hepatic failure is reported to be the most frequent cause of in-hospital death following major hepatectomy[14,20]. This is the reason why hepatobiliary surgery for HC is still recognized as the most difficult besides liver transplantation. Nevertheless, surgical resection with extended hepatectomy, caudate lobectomy, lymphadenectomy, vascular resection, and reconstruction remains the cornerstone of the treatment and represents the only potentially radical therapeutic modality to prolong the survival of patients with HC[21-26].

Uni- and multivariate analyses have identified various prognostic factors for overall survival (OS) and disease-free survival (DFS) of HC[7,27-29]. However, only large-volume patient cases can provide more confidence to guide the treatment. Thus, the current study was planned to determine the following: (1) estimate prognostic factors associated with OS and DFS after successful resection of HC in a large, single-center study; (2) evaluate which factors could contribute to the obtaining of R0 resection to help future surgical decision making; and (3) compare various surgical procedures in treating and prolonging the lifespan of HC patients to guide their treatment and forecast the postoperative prognosis.

MATERIALS AND METHODS

Patients

All patients with a diagnosis of HC that were evaluated and treated at our institution since 1990 were identified from a hepatobiliary database. Patients were divided into three groups: those who underwent curative surgery (n = 381), those who only received palliative surgery (n = 330), and those who did not receive any surgery (n = 103). Patients with intrahepatic bile duct carcinoma infringing the hilum, those with gallbladder carcinomas, and those who underwent liver transplantation were excluded. Clinical, radiologic, histopathologic, therapy, and survival data were obtained and evaluated.

Assessment of resectability

Resectability was assessed both with preoperative imaging studies and intraoperative evaluation. Patients with any of the following were considered to be unresectable: poor conditions, Child-Pugh C, advanced biliary invasion that excludes complete tumor resection, encasement of major vessel structures that eliminate vascular reconstruction, lymph nodes metastases beyond the hepatoduodenal ligament, and metastatic disease (lung and peritoneum metastases)[30,31]. Biliary drainage was performed in most of patients with obstructive jaundice. In patients with cholangitis, resection was performed after alleviation of inflammation. As for the patients who were considered to have potentially resectable tumors, portal vein embolization was performed when the future remnant liver volume (25%-30%) was deemed insufficient (n = 53 patients). Surgical procedures were selected according to the preoperative and intraoperative evaluation.

Follow-up protocol

After treatment, patients were regularly followed-up at an outpatient clinic with clinical examination, serum carbohydrate antigen (CA) 19-9 level, liver function tests, and hepatic ultrasonography. If recurrence was suspected in some specific patients, further assessments such as abdominal CT or magnetic resonance cholangiopancreatography were used to make a definitive diagnosis. The median follow-up period for resected patients was 21.7 mo (range, 3-85 mo) with a follow-up rate of 95.6%.

Statistical analysis

Data analysis was performed using SPSS version16.0 (SPSS Inc., Chicago, IL, United States). Frequency and descriptive analysis were used to depict patient characteristics. Parametric statistical analysis was conducted using a Student's t test, while nonparametric analysis was calculated using a χ^2 test. Survival (calculated from the time of surgery) was estimated using Kaplan-Meier methods, differences in survival were reviewed using the log-rank test. Multivariate analysis was performed on all factors with a P value of less than 0.10 in univariate analysis. Univariate and bivariate analyses were used to check the association of several tumor variables with tumor resection margin. Multiple logistic regression analysis was used in the final analysis to adjust for independent variables for tumor-free margin. The hazard ratio (HR) and the 95%CI were estimated, and a P < 0.05 was considered as significant.

RESULTS

Patients and tumors

The clinical characteristics of the study population are summarized in Table 1. The specific surgical procedures for patients who underwent curative and palliative surgery are presented in Table 2.

Morbidity and mortality

Curative intent surgery: The perioperative complication rate after major surgical treatment was 29.4% (n = 112), which includes, hemorrhage (15 cases), bile leakage (40 cases), peritoneal cavity infection (16 cases), lung infection (23 cases), sepsis (3 cases), acute cardiac failure (3 cases), hepatic failure (20 cases), renal failure (5 cases), stress ulcer (10 cases), wound dehiscence (4 cases), and hydrothorax or ascites (6 cases). The perioperative mortality rate was 3.8% (n = 10). Both postoperative morbidity and operative mortality were deemed as those occurring within 60 d of the major surgery, or occurred at any time during the postoperative hospital stay.

The relationship between postoperative complications and risk factors was evaluated. Patients undergoing hepatectomy had more complications when compared with those who underwent bile duct resection alone (P < 0.001). In patients with postoperative hyperbilirubinemia, the incidence of postoperative complication rate was also higher (P = 0.004).

Palliative intent surgery: The perioperative complication rate after palliative treatment was 11.2% (n = 37), of which the most frequent was lung infection (16 cases), followed by hemorrhage (4 cases), bile leakage (7 cases), peritoneal cavity infection (13 cases), sepsis (2 cases), wound infection (2 cases), hepatic failure (3 cases), renal failure (1 cases), wound dehiscence (1 case), and others (3 cases). The perioperative mortality rate was 4.5% (15 cases), of which the most common cause was multiple organ failure because of liver failure (8 cases), followed by renal failure (3 cases), infective complications (3 cases), and heart failure (1 case).

Survival analysis of curative and palliative surgery

As expected, radical resection provided the best opportunity for OS with a median survival time of 26.3

Table 1 Characteristics of patients receiving curative and palliative surgery n (%)

Variable	Curative surgery (n = 381)	Palliative surgery (n = 330)
Age (median [range])	60 [26-82]	58 [19-80]
Sex, male (%)	231 (60.6)	178 (53.9)
Presenting symptoms		
Jaundice	267 (70.1)	240 (72.7)
Weight loss	26 (6.8)	22 (6.7)
Abdominal pain	24 (6.3)	28 (8.5)
Nausea and vomiting	20 (5.2)	17 (5.1)
General fatigue	44 (11.6)	23 (7.0)
Tumor markers (median [range])		
Preoperative CA 19-9 level, U/mL	348 [0.6-1000]	539.9 [0.6-3015.2]
Preoperative CA 125 level, U/mL	19.84 [1.23-257.70]	33.94 [1.54-1598.00]
Preoperative CEA level, ng/mL	3.23 [0.20-65.51]	4.44 [0.47-1000.00]
Liver functions (median [range])		
Preoperative TB level, umol/L	209.4 [7.1-586.3]	239.65 [1.90-805.70]
Preoperative ALT level, U/L	95 [10-967]	78.5 [6.0-1212.0]
Preoperative AST level, U/L	86 [14-1016]	87 [11-927]
Preoperative Albumin level, g/L	36.7 [18.7-51.8]	35.95 [21.30-72.50]
Preoperative hospital stay (median [range])	7 [2-44]	7 [3-48]
Total hospital stay (median [range])	19 [9-113]	16 [4-102]
Portal vein embolization	53 (13.9)	
Biliary drainage	201 (52.8)	
Estimated blood loss (median [range])	600 [50-2000]	348 [0.6-1000]
Bismuth-Corlette classification		
Type Ⅰ	95 (25.2)	16 (4.8)
Type Ⅱ	92 (24.2)	59 (17.9)
Type Ⅲa or Ⅲb	102 (26.8)	102 (30.9)
Type Ⅳ	92 (24.2)	153 (46.4)

ALT: Alanine aminotransferase; AST: Aspartate transaminase; CA: Carbohydrate antigen; CEA: Carcinoembryonic antigen; TB: Total bilirubin.

Table 2 Type of surgical procedures

Surgical procedures	n (%)
Curative intent surgery	381 (53.6)
Hilar bile duct resection alone	50 (13.1)
Left hemihepatectomy	142 (37.3)
Right hemihepatectomy	101 (26.5)
Left trisegmentectomy	46 (12.1)
Right trisegmentectomy	20 (5.2)
Mesohepatetctomy	22 (5.8)
Additional procedures	
Caudate lobectomy	300 (78.7)
Portal vein resection	51 (13.4)
Pancreatoduodenectomy	8 (2.1)
Palliative intent surgery	330 (46.4)
Surgical palliation	266 (80.6)
Nonsurgical palliation	64 (19.4)
ERCP	35 (10.6)
PTCD	29 (8.8)

ERCP: Endoscopic retrograde cholangiopancreatography; PTCD: Percutaneous transhepatic cholangial drainage.

mo, and the one-, three-, and five-year survival rates were 80%, 43%, and 28%, respectively. This was in contrast to the patients who underwent palliative surgery with a median OS of approximately 7.3 mo, with one-, three-, and five-year survival rates of 10%, 2%, and 0%, respectively (Figure 1, log-rank test, P < 0.001). As for patients who did not receive any surgical treatment, the median OS and the one- and three-year survival rates were 2.6 mo and 1% and 0%,

respectively (Figure 1, log-rank test, P < 0.001). The median DFS for the radical resection group was 18.1 mo, and the one-, three-, and five-year DFSs were 78%, 18%, and 10% respectively. Furthermore, we compared the survival rate of those who underwent surgical palliation and nonsurgical palliation; the former had a median survival time and 6-mo survival rate of 7.4 mo and 27% respectively, while the latter had a median survival time of 5.5 mo and 6-mo survival rate of 9% respectively (P < 0.001).

Factors associated with OS and DFS after curative resection

As is shown in Table 3, OS was significantly longer in patients with no lymph node metastasis (P < 0.001), well histologic differentiation (P < 0.001), negative resection margin (P < 0.001), tumor size ≤ 3 cm (P < 0.001), caudate lobectomy (P = 0.04), lower CA 19-9 level (P = 0.039), and no vascular invasion (P = 0.009). Hepatectomy and the lack of perineural infiltration approached statistical differences as positive prognostic factors for OS in univariate analysis (P = 0.072 and 0.084 respectively). The factors associated with disease-free survival were also examined. Resection margins (P < 0.001), tumor differentiation (P < 0.001), lymph nodes metastases (P < 0.001), tumor size (P < 0.001), caudate lobectomy (P < 0.001), CA 19-9 level (P = 0.018), American Joint Committee On Cancer (AJCC) T stage (P = 0.028), and vascular invasion (P < 0.001)
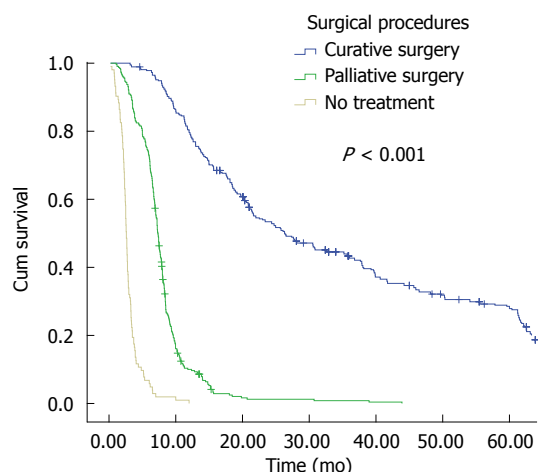
Figure 1 Cumulative overall survival of patients who underwent curative intent surgery, palliative surgery, and those who did not receive any treatment for hilar cholangiocarcinoma.

were associated with DFS (Table 3).

In multivariate analysis, tumor size > 3 cm (HR = 1.482, 95%CI: 1.127-1.949; P = 0.005), positive nodal disease (HR = 1.701, 95%CI: 1.346-2.149; P < 0.001), poor differentiation (HR = 2.535, 95%CI: 1.839-3.493; P < 0.001), vascular invasion (HR = 1.542, 95%CI: 1.082-2.197; P = 0.017), and positive margins (HR = 1.798, 95%CI: 1.314-2.461; P < 0.001) remained associated with OS. For DFS, positive nodal disease (HR = 3.383, 95%CI: 2.633-4.348; P < 0.001), poor differentiation (HR = 2.774, 95%CI: 2.012-3.823; P < 0.001), vascular invasion (HR = 2.136, 95%CI: 1.658-3.236; P < 0.001), and positive margins (HR = 1.835, 95%CI: 1.256-2.679; P < 0.001) were correlated as determined by the multivariate analysis.

Factors associated R0 resection

R0 resection was found to confer to a median survival time of 35.2 mo, while patients with R1 and R2 resections had a median survival time of 12.4 mo, and the palliative surgery only granted a median survival time of 7.3 mo. Thus, further studies emphasized the factors that could affect the tumor-free margin. Univariate analysis showed that tumor differentiation (P = 0.001), tumor diameter (P < 0.001), hepatectomy (P = 0.012), lymph node metastasis (P = 0.001), AJCC T stage (P = 0.001) caudate lobectomy (P = 0.001), Bismuth-Corlette classification (P = 0.038), and vascular invasion (P = 0.010) were associated with tumor-free margin. Multiple logistic regression analysis showed that caudate lobectomy [odds ratio (OR) = 9.771, 95%CI: 4.672-20.433; P < 0.001], tumor diameter (OR = 3.772, 95%CI: 1.914-7.434; P < 0.001), surgical procedures (OR = 10.236, 95%CI: 4.738-22.116; P < 0.001), AJCC T stage (OR = 2.010, 95%CI: 1.043-3.870; P = 0.037), and vascular invasion (OR = 2.278, 95%CI: 0.997-5.207; P = 0.051) were independently associated with tumor-free margin after adjusting for other factors.

DISCUSSION

HC remains among the most difficult management problems faced by surgeons. The accumulated outcomes from many institutions show confidently that only an excision with negative resection margin can be regarded as radically therapeutic, and in this condition, hepatic resection is often demanded[28,30]. Many authorities have reported various prognostic factors of HC; however, due to the differences in study methods and small patient numbers in other studies, potential biases or even contradictory outcomes may result. Furthermore, some large cases of multi-center reports may also induce biases due to the heterogeneity of clinical methods and surgical strategies. Thus, a large number of HC cases from a single center are urgently needed to standardize the prognostic factors and to supply better guidance and treatment for HC.

We report a median OS of 26.3 mo, with the one-, three-, and five-year survival rates of approximately 80%, 43%, and 28%, which are comparable to some published articles from high-volume hepatobiliary centers reporting a median OS of 16-40 mo, and a five-year survival rate of 11%-40%[4,32-34]. We also report a median DFS of 18.1 mo for the radical resection group, which is within the range of 12 mo to 20 mo covered by other literature[1,4,31,35]. The data in our series has also verified the common notion that curative surgery provides the best opportunity to increase the median and long-term survival rates of patients diagnosed with HC, as the failure of conducting curative surgery resulted in a sharp and signficant decrease in the OS. Compared with patients who did not accept any treatment, palliative surgery resulted in a relatively better outcome, which might be explained as follows. Palliative surgery can remove the root of obstructive jaundice and adequately open the biliary tract, thus, liver function can be improved. We also identified that intraoperative palliation conferred a relatively longer survival than nonsurgical palliation, and can lessen the odds of bile duct obstruction by opening the bile duct as much as possible, facilitating whole biliary decompression, and enhancing liver function. Therefore, we believe that intraoperative palliation is superior to nonsurgical palliation in patients who do not undergo curative resection. However, further studies with larger numbers of cases are needed to confirm this. In the long run, compared with curative surgery, we believe that curative surgery is the best way to prolong survival.

Many clinical, surgical, and pathologic factors have recently been shown to influence OS and DFS after major resection[28,29,31,36]. In our retrospective study, multivariate analysis showed that surgical margin, lymph node, tumor differentiation, and vascular invasion were independent factors for OS and DFS. In addition, tumor size was also an independent factor for OS, but not for DSF.

It is widely recognized that among a large

Table 3 Univariate analysis of prognostic factors for OS and DFS

Variables	Median OS (mo)	*P* value	Median DFS (mo)	*P* value
Tumor size				
≤ 3 cm	35.2	< 0.001	19.8	< 0.001
> 3 cm	14.7		13.0	
Surgical procedures				
BDR	20.8	0.072	15.0	0.065
BDR + hepatectomy	27.6		18.7	
Lymph node metastasis				
N0	39.9	< 0.001	25.4	< 0.001
N1-2	15.7		12.3	
Tumor differentiation				
Well	54.1	< 0.001	25.3	< 0.001
Moderate	27.6		17.8	
Poor	13.5		12.1	
Resection margin				
R0	35.2	< 0.001	20.6	< 0.001
R1 and R2	12.4		9.6	
Presence of vascular invasion				
No	26.3	0.009	19.0	< 0.001
Yes	20.9		10.6	
Caudate lobe resection				
Yes	35.7	0.040	21.3	< 0.001
No	21.4		15.0	
CA 19-9 > 100 U/L				
No	39.7	0.039	23.6	0.018
Yes	23.0		16.7	
Perineural infiltration				
No	27.3	0.084	22.7	0.090
Yes	20.8		15.9	
T stage (AJCC)				
T1 and T2	27.6	NS	19.2	0.028
T3 and T4	25.7		16.9	

Additional factors not significant in univariate analysis included age, sex, gross feature, operative time, total hospital stay, preoperative biliary drainage, and Bismuth-Corlett classification. AJCC: American Joint Committee on Cancer; BDR: Hilar bile duct resection; CA: Carbohydrate antigen; DFS: Disease-free survival; NS: Not significant; OS: Overall survival.

succession of prognostic factors for HC, tumor-free margin is the most powerful predictor for both OS and DFS[35,37,38]. In our present study, R0 resection emerged as an independent prognostic factor for both OS (Figure 2A) and DFS (Figure 3A); patients with negative margins had markedly better OS and DFS than those with positive ones. The fact that patients undergoing R1 or R2 resection have better outcomes than patients undergoing palliative surgery has also been confirmed in current research. We further examined factors associated with R0 resection, finding that patients with smaller tumor size, concomitant hepatic resection, caudate lobectomy, T1 and T2 stage, and the lack of vascular invasion had a higher likelihood of obtaining tumor-free margin.

In our study, survival was affected by the existence of lymph node metastasis as testified by univariate and multivariate analyses, with a decrease in the median OS from 39.9 mo to 15.7 mo, and a decrease in the median DFS from 25.4 mo to 12.3 mo. These correspond with times reported by previous studies, in which lymph node metastasis was an important independent prognostic factor for both DFS[31,39,40] and OS[26,28,39,41,42]. The prognostic significance of node status stresses the necessity for radical

lymphadenectomy. In this respect, thorough lymph nodes dissection may be important, and should be prospectively evaluated and studied in the future.

Tumor differentiation is a disputable factor in many retrospective studies. Hasegawa *et al*[42] did not find a survival disadvantage in cases of tumor differentiation, while Saxena *et al*[4] have shown that tumor differentiation is a biologic marker for measuring tumor invasion and metastasis and predicting long-term survival, which is comparable to our results, as the median OS decreased sharply from 54.1 mo to 13.5 mo when the patients had poor differentiation. The median DFS of patients with well-differentiated tumors was twofold greater than those with poor-differentiated tumors. Thus, in view of the fact that histologic differentiation is an independent prognostic factor for both OS and DFS, we are tempted to conclude that poorly differentiated cancers have a poor prognosis and higher recurrence rate.

Vascular invasion is no longer a contraindication for the excision of HC. As this procedure has a high mortality and risk, we performed vascular resection and reconstruction only in patients with clinically suspected vascular infiltration. Our report demonstrates that patients with vascular invasion are
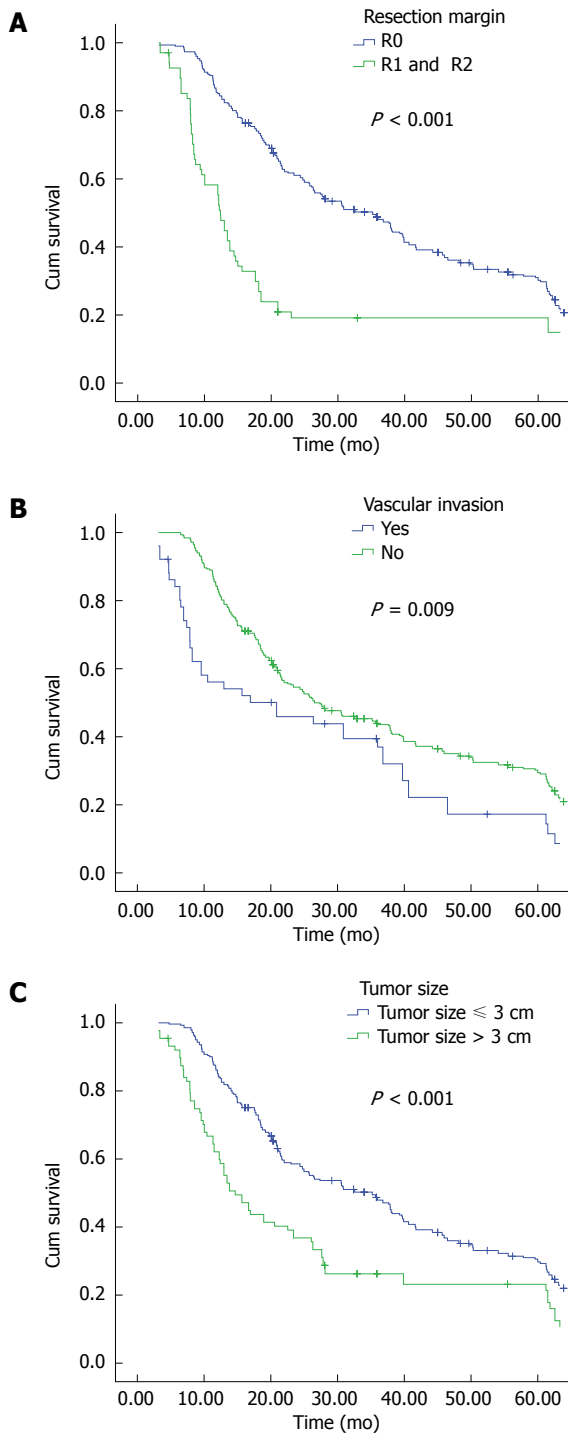
Figure 2 Cumulative overall survival of patients who underwent curative surgery for hilar cholangiocarcinoma stratified by A: Resection margin; B: Vascular invasion; and C: Tumor size.
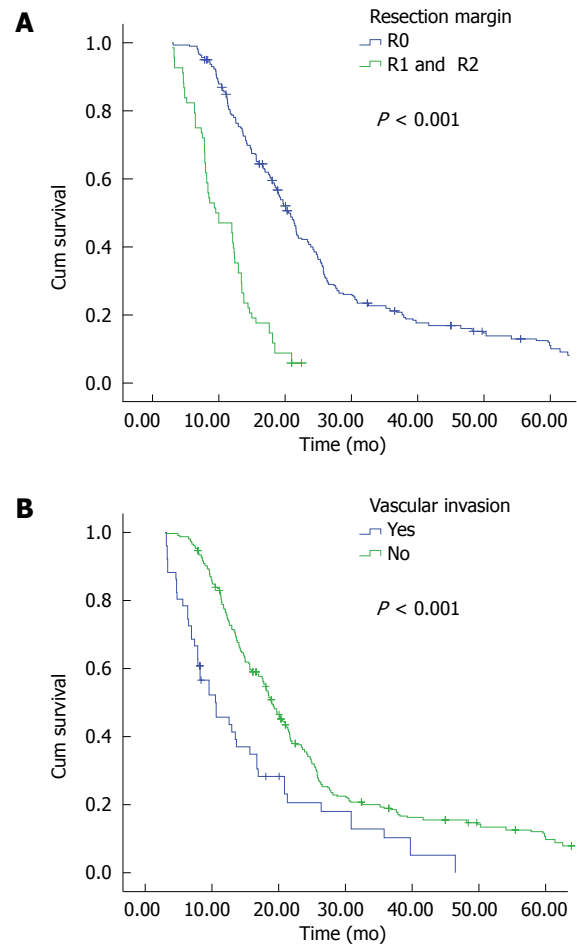

Figure 3 Disease-free survival of patients who underwent curative surgery for hilar cholangiocarcinoma stratified by A: Resection margin; and B: Vascular invasion.

independent factor associated with OS in multivariate analysis (Figure 2C). So far, no other reports have shown this association as clearly as the results of the present study. The findings also confirmed that T stage of the DeOliveira staging system, in which the 3-cm cutoff was regarded as T3, is important. Moreover, tumor size influenced R0 resection in multivariate logistic regression analysis. Thus, from this point of view, tumor size needs to be taken into consideration when evaluating the long-term survival of HC patients.

Many studies have shown that caudate lobectomy appears to have a positive effect on tumor-free margin and survival after resection of Klatskin tumors[26,43,44]. In our study, caudate lobes were routinely removed, which was not associated with postoperative complications, and the OS and DFS were significantly longer in these patients as compared with those without caudate lobectomy in the univariate analysis. At the same time, caudate lobectomy approached statistical significance as a positive prognostic factor for OS on multivariate analysis. Furthermore, it was also an independent factor for tumor-free margin in our current series. Thus, we firmly believe that this procedure should be considered as a part of the

more likely to have a poor OS and DFS (Figures 2B and 3B); similarly, vascular invasion was also associated with a higher tendency of R1 and R2 status, though it only approached statistical difference multivariate logistic regression. Thus, in those highly suspected patients, vascular resection is recommended.

Perhaps more importantly, we found that tumor size was a significant prognostic parameter for OS and DFS in the univariate analysis. It was also an

standard surgical resection.

In contrast to previous studies, a survival advantage was not observed in case of hepatectomy. We only found that curative surgery accompanied with hepatectomy achieved more complete tumor-free margins, which is consistent with many previous studies[27,29,43,45]. Tumor-free margin, in turn, could promote OS and is a powerful predictor of survival, both reported in our series and in other literature. In our research, hepatectomy was the most important factor that could affect the tumor-free margin. Thus hepatectomy is an indirect prognostic factor that can promote OS by influencing the tumor resection margin.

In conclusion, radical surgical resection is the best treatment option for HC. R0 resection along with negative lymph nodes metastases, well differentiation, and lack of vascular invasion indicate better OS and DFS. Smaller tumor size also predicts better OS, but not DFS. Multivariate logistic regression analysis shows that hepatectomy, tumor diameter, T stage, caudate lobectomy, and vascular invasion are independently associated with tumor-free margin. Hepatectomy can help achieve more tumor-free resection margins and then indirectly affect OS; it is an indirect prognostic factor for survival.

COMMENTS

Background
Many authorities have reported various prognostic factors for hilar cholangiocarcinoma (HC); however, due to the difference in study methods and small patient numbers, these studies may be biased or have contradictory outcomes. Furthermore, some large multi-center reports could be biased due to the heterogeneity of clinical methods and surgical strategies.

Research frontiers
This large, single-center study estimates prognostic factors associated with overall survival (OS) and disease-free survival (DFS) after successful resection of HC to identify those that could contribute to R0 resection. These findings will help future surgical decision making in the treatment of HC.

Innovations and breakthroughs
Based on our study, R0 resection along with negative lymph nodes metastases, well differentiation, and lack of vascular invasion indicated better OS and DFS. Smaller tumor size also predicts better OS, but not DFS. Hepatectomy, tumor diameter, T stage, caudate lobectomy, and vascular invasion were independently associated with tumor-free margin. Hepatectomy can help achieve more tumor-free resection margins and indirectly affect OS; it was an indirect prognostic factor for survival.

Applications
HC remains among the most difficult management problems faced by surgeons. These results may help future surgical decision making to better guide the treatment of HC.

Terminology
Curative resection is important for the prognosis of HC, and R0 resection plays a significant role in prolonging the survival time of patients. R0 resection refers to those with microscopically negative tumor resection margin.

Peer-review
The authors examined the potential risk factors correlated with HC and factors that could affect tumor-free margin in a large, single-center study. The study was well performed and its findings are interesting and informative.

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