ORIGINAL ARTICLE

Prognostic analysis and outcome of hilar cholangiocarcinoma after radical resection: a retrospective study

Análisis pronóstico y resultado del colangiocarcinoma hiliar tras la resección radical: un estudio retrospectivo

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Abstract

Objectives: *The predictive factors affecting the survival of hilar cholangiocarcinoma (HC) are ambiguous. This study aimed to identify the predictors and recurrence patterns of HC.* **Methods:** *A retrospective analysis of the clinicopathological findings of 126 patients with HC from 2009 to 2019 was performed.* **Results:** *The proportion of Bismuth I and II HC in the recurrence group was higher than that in the non-recurrence group ($p < 0.01$). The recurrence group had poorer tumor differentiation, a more advanced N stage, and a higher incidence of perineural invasion compared with the non-recurrence group. N stage and tumor differentiation were independently associated with disease-free and overall survival of patients ($p < 0.01$). Bile duct resection (BDR) combined with hepatectomy was more favorable to disease-free and overall survivals than BDR alone in Bismuth I and II HC, although p values were marginal ($p = 0.072$ and $p = 0.045$). A higher proportion of patients in the non-recurrence group underwent BDR combined with hepatectomy than that in the recurrence group ($p < 0.01$).* **Conclusions:** *N stage and tumor differentiation are the two independent predictors of patient survival. BDR combined with hepatectomy is recommended for patients with Bismuth I and II hilar cholangiocarcinoma.*

Keywords: *Hilar cholangiocarcinoma. Bismuth classification. Survival. Bile duct resection. Hepatectomy.*

Resumen

Objetivos: *Los predictores que afectan a la supervivencia del colangiocarcinoma hiliar son ambiguos. Este estudio tiene como objetivo identificar los factores predictivos y los patrones de recurrencia del colangiocarcinoma hiliar.* **Métodos:** *Se aplicó un análisis retrospectivo con126 pacientes con colangiocarcinoma hiliar desde 2009 hasta 2019.* **Resultados:** *La proporción de colangiocarcinoma hiliar Bismuth I y II en el grupo de recurrencia fue mayor que en el grupo de no recurrencia ($p < 0.01$). El tumor del grupo de recidiva tenía un estadio N más avanzado que el del grupo de no recidiva. El estadio N se asocia de forma independiente con la supervivencia libre de enfermedad y global del paciente ($p < 0.01$). La resección de la vía biliar combinada con la hepatectomía benefició más a la supervivencia libre de enfermedad y global que la resección de la vía biliar sola en el colangiocarcinoma hiliar ($p = 0.072$ y $p = 0.045$). Una mayor proporción de pacientes se sometió a resección de la vía biliar combinada con hepatectomía en el grupo de no recidiva que en el de recidiva ($p < 0.01$).* **Conclusiones:** *El estadio N fue el predictor independiente. Se recomienda la resección de la vía biliar combinada con hepatectomía para los pacientes con colangiocarcinoma hiliar Bismuth I y II.*

***Palabras clave*:** *Colangiocarcinoma hiliar. Clasificación de Bismuth. Supervivencia. Resección de la vía biliar. Hepatectomía.*

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Introduction

Surgical resection is the only strategy to improve survival rates for hilar cholangiocarcinoma (HC), even though, the 5-year survival rate of HC is unsatisfactory, ranging from approximately 14% to 45%[1,2]. Despite the advances in surgical techniques and perioperative supportive care, the treatment of HC remains challenging. Due to its longitudinally extended infiltrative nature and proximity to vital vascular structures, surgical resection of HC is limited and has unfavorable oncological outcomes[3,4]. Extended major hepatectomy with concomitant vascular and biliary resection and reconstruction is associated with high perioperative morbidity and mortality rates, and thus, the evolution of surgical management for HC is ongoing. Predictors reported in some previous studies include resection margins, tumor differentiation, and lymph node metastasis[5,6]. These studies identified a wide range of prognostic factors due to the variation of the follow-up period, including palliative or numerous surgical approaches and R1 resection. Therefore, at present, the predictive factors affecting the survival of HC are ambiguous. The aim of this study is to investigate the predictors and recurrence patterns of HC in a large cohort of patients who underwent R0 resection and had long-term follow-ups.

Methods

Patients

The data of 126 consecutive patients with HC from January 2009 to December 2019 at two hospitals were retrospectively reviewed. Computed tomography (CT) and magnetic resonance imaging (MR) were used to assess tumor infiltration. PET-CT was used to detect suspected distant metastases. Endoscopic ultrasound was also suggested to evaluate biliary and vascular involvement. If patients had obstructive jaundice, endoscopic nose biliary drainage through endoscopic retrograde cholangiopancreatography or percutaneous transhepatic biliary drainage was routinely performed. This study was approved by the hospital's ethics committee, under the approval number 2008-117-(1), and was conducted according to the principles outlined in the Declaration of Helsinki. Each patient provided a written informed consent.

Surgical procedures

During this procedure, bile duct resection (BDR) was routinely performed with both the proximal and distal bile duct margins examined by frozen examination. Resection margins of the distal bile duct and proximal hepatic duct were sent for frozen-section examination during operation. R1 resection was obtained when the resection margin (distal bile duct or proximal hepatic duct or both) was not free from cancer cells under microscope observation. Re-resection of the bile duct or hepatectomy was performed if the bile duct margin was positive on frozen section analysis. All 126 patients underwent R0 resection approved by the frozen section analysis. Lymphadenectomy was also performed by skeletonizing the hepatoduodenal ligament as well as harvesting the lymph nodes along the common hepatic artery and retro-pancreatic region. Other lymph nodes are removed only if they are found to be enlarged or positive on pre-surgical imaging. Overall, however, whether and how a BDR or hepatectomy was performed depended largely on the decision of the surgeon. Complications were ranked in accordance with Clavien–Dindo classifications[7]. T and N staging was performed following the American Joint Committee on Cancer 8th edition. Chemotherapy (gemcitabine+cisplatin) was administered to patients with lymph node metastasis if they did not refuse, and those with R1 resection received 5-FU-based concurrent chemoradiotherapy.

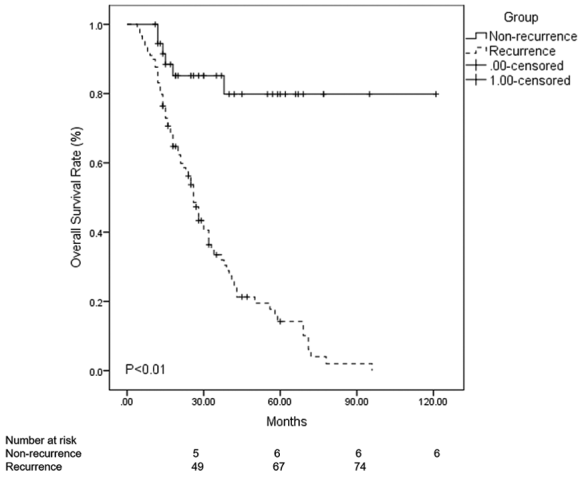

Figure 1. *Comparison of overall survival between non-recurrence and recurrence groups (p < 0.01).*

Follow-up

Patients were followed up at a 3-month frequency during this decade, including a physical examination and a laboratory test. CT or MR was arranged every 3 months for the 1st year and then every 6 months for

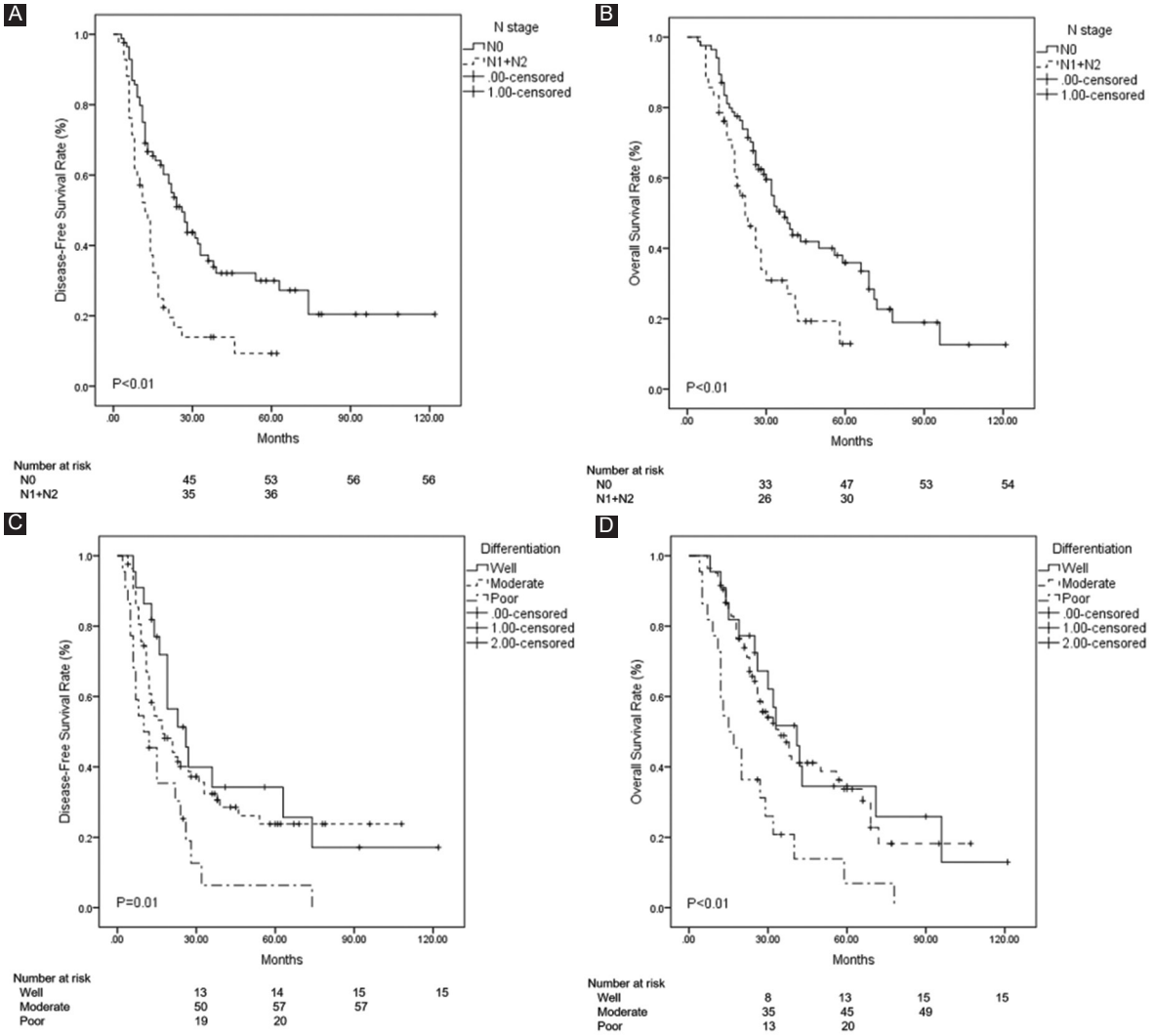

Figure 2. *Comparison of survivals in non-recurrence and recurrence groups.* **A** *and* **B:** *the disease-free and overall survivals shortened dramatically with the advancement of N stage (p < 0.01).* **C** *and* **D:** *patients with poor tumor differentiation had the worst disease-free and overall survivals than those with moderate and well differentiation (p = 0.01 and p < 0.01).*

the 2nd year. CT of the thorax, bone scan, and MR of the brain were performed if clinical examination led to a suspicion of metastasis or PET-CT was performed if other metastases were suspected. The primary endpoint of the study was recurrence. The secondary endpoints were disease-free survival and overall survival. Recurrence was defined as suspicious or confirmed lesions on imaging or histological examination.

Statistical analysis

Continuous variables were expressed as median and range or mean ± standard deviation, whereas categorical variables were expressed as number and percentage. Chi-squared test was used for nominal data. Univariate analysis with χ^2 test or Fisher's exact test was used for categorical variables. When the data did not follow normal distributions, the nonparametric Mann-Whitney U-test was applied. Kaplan-Meier survival was compared using log-rank test. Univariate and multivariate analyses were analyzed through Cox proportional hazard regression. Significance was considered at $p < 0.05$. SPSS 22 (SPSS, Chicago, IL) was used for statistics.

Results

Baseline and clinicopathological features of HC patients

Thirty-seven patients were included in the non-recurrence group while 89 patients were found to have a

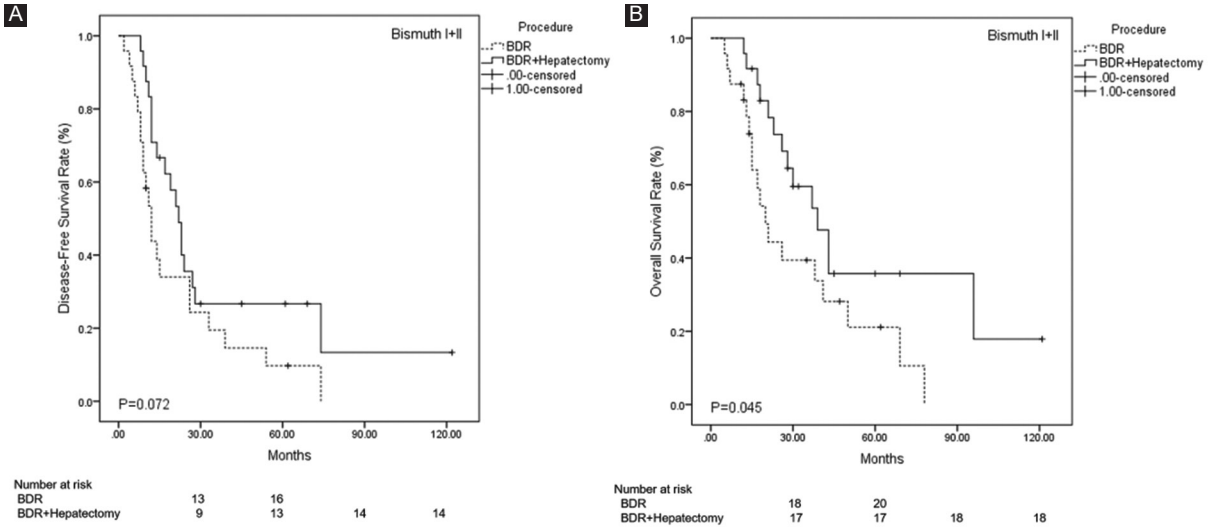

Figure 3. A *and* **B***: survival analysis stratified by surgical strategy in Bismuth I and II hilar cholangiocarcinoma patients. Bile duct resection combined with hepatectomy benefited the disease-free and overall survivals more than BDR alone in Bismuth I and II hilar cholangiocarcinoma (p = 0.072 and p = 0.045).*

recurrence during follow-up. None of the patients in these two groups underwent additional portal vein or hepatic artery resection. No differences were detected between the two groups in terms of age, gender, laboratory tests, proportion of preoperative biliary drainage, proportion of transfusions, incidence of serious surgical complications, and length of hospital stay. Noticeably, the proportion of Bismuth I and II HC was significantly higher in the recurrence group than that in the non-recurrence group (43.8% vs. 24.3%, $p < 0.01$). In addition, the recurrence group had poorer tumor differentiation, a more advanced N stage, and a higher incidence of perineural invasion compared to the non-recurrence group. No differences were observed in other clinicopathological features between the two groups (Table 1).

Survival analysis in non-recurrence and recurrence groups

Overall survival was significantly worse in the recurrence group than in the non-recurrence group ($p < 0.01$) (Fig. 1). In both univariate and multivariate analyses, N stage and tumor differentiation were independently associated with disease-free and overall survival of patients (Tables 2 and 3). Disease-free and overall survivals decreased dramatically with the advancement of N stage ($p < 0.01$) (Fig. 2A and B). Patients with poorly differentiated tumors had the worst disease-free and overall survivals than those of moderate and well differentiation ($p = 0.01$ and $p < 0.01$) (Fig. 2C and D).

Patterns of postoperative recurrence

In the recurrence group, local lymph node recurrence was identified to occur more frequently than local anastomosis recurrence, vascular recurrence, isolated locoregional recurrence, distant recurrence, and other recurrences. For distant recurrences, lung metastasis occurred more frequently, followed by liver, abdomen wall, brain, and bone metastasis (Table 4).

Survival analysis stratified by surgical strategy in Bismuth I and II HC patients.

We found that the proportion of Bismuth I and II HC in recurrence group was larger than that of the non-recurrence group. Hence, we further determined the factors that contributed to this difference. It was found that the surgical strategy contributed to this difference. BDR combined with hepatectomy was more beneficial than BDR alone for the disease-free and overall survival in Bismuth I and II HC, although the p value was marginal ($p = 0.072$ and $p = 0.045$) (Fig. 3A and B). Moreover, in the non-recurrence group, a larger proportion of patients underwent BDR combined with hepatectomy than that in recurrence group ($p < 0.01$) (Table 5).

Discussion

HC is a relatively rare cancer with an extremely poor prognosis. Radical hepatectomy is the only

Table 1. Baseline features of patients with hilar cholangiocarcinoma

Variables	Non-recurrence (n = 37)	Recurrence (n = 89)	p value
Age (mean ± SD)	62.1 ± 6.4	61.5 ± 7.8	NS
Sex (male) (n, %)	27 (73.0)	67 (75.3)	NS
BMI (kg/m2) (mean ± SD)	21.1 ± 3.1	23.2 ± 2.4	NS
Hb (g/dL, mean ± SD)	15.3 ± 2.3	14.7 ± 2.8	NS
Albumin (g/dL, mean ± SD)	3.8 ± 0.5	3.9 ± 0.5	NS
Bilirubin (mg/dL, mean ± SD)	1.9 (0.3-3.2)	2.1 (0.4-4.4)	NS
CEA (median, range)	3.2 (0.3-43.4)	4.0 (0.6-39.2)	NS
CA199 (median, range)	121.6 (2.2-2220.0)	132.1 (4.5-2490.0)	NS
Biliary drainage (n, %)	7 (18.9)	15 (16.9)	NS
Transfusion (n, %)	6 (16.2)	14 (15.7)	NS
Complication (≥ IIIa) (n, %)	2 (5.4)	6 (6.7)	NS
Hospital stay (days, mean ± SD)	24.2 ± 12.5	22.5 ± 10.6	NS
Tumor size (cm, mean ± SD)	3.5 ± 1.9	3.8 ± 1.1	NS
Bismuth type (n, %)			
I + II	9 (24.3)	39 (43.8)	
III + IV	28 (75.7)	50 (56.2)	< 0.01
T stage (n, %)			
1	1 (2.7)	3 (3.4)	
2	26 (70.3)	64 (71.9)	
3	8 (21.6)	18 (20.2)	
4	2 (5.4)	4 (4.5)	NS
N stage (n, %)			
0	31 (83.8)	54 (60.7)	
1	5 (13.5)	29 (32.6)	
2	1 (2.7)	6 (6.7)	< 0.01
Differentiation (n, %)			
Well	8 (21.6)	10 (11.2)	
Moderate	25 (67.6)	51 (57.3)	< 0.01
Poor	4 (10.8)	28 (31.5)	
Lymphovascular invasion (n, %)	8 (21.6)	18 (20.2)	NS
Perineural invasion (n, %)	23 (62.2)	67 (75.3)	< 0.05
Adjuvant therapy (n, %)	7 (18.9)	20 (22.5)	NS

NS: not significant; Hb: hemoglobin; CEA: carcinoembryonic antigen; CA199: cancer antigen 199.

curative treatment strategy for HC. Surgeons have made tremendous efforts to perform an aggressive surgical approach in spite of technique difficulties[8,9]. Despite the efforts to improve the prognosis of HC, the 5-year survival rate remains low[10]. In the past few years, several prognostic factors such as tumor differentiation, lymph node status, and resection margin have been identified. However, the predictive factors for HC are still ambiguous presently. We designed this study to investigate the predictors and recurrence patterns of HC using of a large cohort. We divided the study cohort into a non-recurrent and a recurrence group to compare the recurrence patterns and predictors of HC. As a result, we did find similar results to those previously reported[5,6]. First, the recurrence group had poorer tumor differentiation, a higher incidence of perineural invasion, and a more advanced N stage compared to the non-recurrence group. Second, in both univariate and multivariate models, N stage and tumor differentiation were

Table 2. Univariate and multivariate analysis of the risk factors associated with patients' disease-free survival

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	p value	HR	95% CI	p value
Biliary drainage	0.32	0.11-2.09	NS			
Transfusion	1.21	0.24-4.42	NS			
Complication (≥ IIIa)	1.33	0.36-5.31	NS			
Tumor size (≥ 3cm)	0.68	0.33-2.55	NS			
Bismuth type	0.86	0.25-1.31	NS			
T stage	2.33	0.76-3.44	NS			
N stage	3.23	2.12-4.37	< 0.01	3.27	1.87-4.50	< 0.01
Differentiation	2.72	1.49-3.58	< 0.01	1.87	1.21-2.80	< 0.01
Lymphovascular invasion	0.49	0.10-2.56	NS			
Perineural invasion	3.13	0.29-4.86	NS			
Adjuvant therapy	0.36	0.12-5.22	NS			

NS: not significant ; HR: hazard ratio; CI: confidence interval.

Table 3. Univariate and multivariate analysis of the risk factors associated with patients' overall survival

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	p value	HR	95% CI	p value
Biliary drainage	0.29	0.03-3.12	NS			
Transfusion	2.5	0.25-3.36	NS			
Complication (≥ IIIa)	2.03	1.03-4.44	< 0.05			
Tumor size (≥ 3cm)	0.91	0.46-1.91	NS			
Bismuth type	3.11	0.27-5.85	NS			
T stage	2.20	0.60-3.97	NS			
N stage	2.05	1.12-3.28	< 0.01	3.11	1.60-4.24	< 0.01
Differentiation	2.91	1.78-5.38	< 0.01	2.22	1.10-4.76	< 0.01
Lymphovascular invasion	2.02	0.72-3.85	NS			
Perineural invasion	1.40	0.26-2.84	NS			
Adjuvant therapy	2.22	0.22-3.34	NS			

NS: not significant; HR: hazard ratio; CI: confidence interval.

independently associated with disease-free and overall survival, which decreased sharply as N stage advanced. Third, patients with poorly differentiated tumors had the worst disease-free and overall survival than those with moderate and well differentiation. Fourth, noticeably, we found that the proportion of Bismuth I and II HC in the recurrence group was higher than that in the non-recurrence group with a great significance, which has not been reported in previous investigations.

We further tried to identify possible answers that could explain this new finding. Previously, there was no survival advantage for HC patients undergoing aggressive surgical approaches due to high mortality[11]. However, with the advances in surgical techniques and preoperative management, this condition has changed a lot.

Table 4. Patterns of postoperative recurrence

	Recurrence (n = 89) (n, %)
Locoregional metastasis (n, %)	
Local lymph node	40 (44.9)
Local anastomosis site	13 (14.6)
Hepatic and portal vessels	4 (4.5)
Isolated locoregional recurrence (n, %)	30 (33.7)
Distant metastasis (n, %)	
liver	5 (5.6)
Abdomen wall	5 (5.6)
brain	3 (3.4)
lung	7 (7.9)
bone	1 (1.1)
Others (n, %)	3 (3.4)

Table 5. Surgical procedure of Bismuth I and II hilar cholangiocarcinoma

Surgical procedure	Non-recurrence (n = 9) (n, %)	Recurrence (n = 39) (n, %)	p value
BDR	3 (33.3)	21 (53.8)	
BDR + hepatectomy	6 (66.7)	18 (46.2)	< 0.01

BDR: bile duct resection.

Mortality rates have become acceptable and survival benefits have been achieved[9,12,13]. BDR combined with hepatectomy is now a standard procedure for Bismuth III and IV HC, but the benefit of hepatectomy in Bismuth I and II HC remains controversial. A few investigations have suggested that BDR alone was sufficient for Bismuth I and II HC. Otani et al. found that the R0 resection rate and overall survival were similar between local resection for Bismuth I and II HC and combined hepatectomy for Bismuth III and IV HC[14]. Chen et al. also demonstrated no diversity in long-term survival and recurrence between the two groups[15]. However, the sample size was relatively small, and thus, selection bias might exist in these studies. In the present study, we found that BDR combined with hepatectomy was beneficial to the disease-free and overall survival in patients with Bismuth I and II HC though the p value was marginal. Nakanishi et al. recommend left hepatectomy for Bismuth type I and II HC without extra ductal tumor invasion in the right side of the hepatic portal region[16]. However, Zhang et al. found that similar rates of R0 resection were achieved among patients who had BDR versus BDR+ hepatectomy for Bismuth I and II HC. The addition of hepatectomy with or without caudate lobectomy did not result in any survival or recurrence benefits than BDR alone, as long as R0 margin was achieved[17]. The main limitation of these retrospective studies is the small sample size. We suggest that the need for hepatectomy for Bismuth I and II is condition dependent. Once R0 margin can be achieved and evaluated by the surgeon, hepatectomy is an alternative option. However, future large multicenter studies are still needed to define the optimal surgical strategies for patients with Bismuth type I and II HC. Recent studies pointed out that a positive radial margin is the common cause of R1 resection and has a negative impact on survival[18]. Similarly, we found a larger proportion of patients who underwent BDR combined with hepatectomy in non-recurrence group than that in recurrence group in the present study of R0 resection patients. Therefore, we believe that more aggressive surgical strategies, such as combined hepatectomy, are critical to achieve R0 resection and improve the survival of Bismuth I and II HC. In addition, local lymph node recurrence was identified to occur more frequently than other recurrences, so we suggest an extensive regional lymph node dissection contributing to curative resection. In summary, it comes into view that the contents mentioned above may support the possibility that a larger proportion of Bismuth I and II HC occupies the recurrence group.

As for the issue of vascular resection, if resection and reconstruction are possible, combined vascular resection can be performed with an acceptable mortality rate and can offer long-term survival to some patients with advanced HC previously considered inoperable[19,20]. Combined procedures should be encouraged as an option to cure intractable disease as suggested by a meta-analysis[21]. Nowadays, surgical treatment of HC has steadily evolved, with decreasing mortality and increasing survival rates. Previous reports have emphasized lymph node metastasis, histopathologic status, resection margin, and adjuvant chemotherapy as important prognostic factors for HC[22-25]. Moreover, recent studies have recommended adjuvant chemotherapy conducted as a bridge modality to improve radical resection rates in locally advanced HC[26,27]. However, in the present study, we did not find the survival benefit of adjuvant chemotherapy in both univariate and multivariate analyses. Therefore, we advocate that the impact of surgical technique and approach remains important in such malignant tumors.

Conclusions

This study had some limitations because of its retrospective design. Although there were limitations,

the new findings of the present study are remarkable and may have some impact on the current guidelines and contribute to the clinical practice in the following aspects. First, N stage and tumor differentiation are the two independent predictors of survival in patients with HC. Second, local lymph node recurrence is the predominant pattern of recurrence in HC. Therefore, we recommend extensive regional lymph node dissection to facilitate curative resection. Third, at present, however, we recommend BDR combined with hepatectomy for patients with Bismuth I and II HC.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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