



# Long-term outcome and prognostic factors of intrahepatic cholangiocarcinoma involving the hepatic hilum versus hilar cholangiocarcinoma after curative-intent resection: Should they be recognized as perihilar cholangiocarcinoma or differentiated?



Jiong Lu, Bei Li, Fu-Yu Li, Hui Ye, Xian-Ze Xiong, Nan-Sheng Cheng\*

Department of Bile Duct Surgery, West China Hospital, Sichuan University, Chengdu, Sichuan Province, China

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## ABSTRACT

**Background:** Perihilar cholangiocarcinoma is defined as tumors arising predominantly at or near the biliary confluence, potentially consisting of two types: hilar cholangiocarcinoma (HC) and intrahepatic cholangiocarcinoma involving the hepatic hilum (hICC). However, whether hICC and HC should be strictly distinguished or combined remains highly controversial. We aimed to compare the clinicopathological characteristics, prognostic factors and long-term outcome of hICC versus HC after curative-intent resection.

**Methods:** Between January 1998 and June 2015, a total of 325 patients with hICC (n = 146) and HC (n = 179) who underwent curative-intent resection were enrolled. The medical records of these patients were retrospectively reviewed.

**Results:** Portal vein invasion, larger tumors, and later T stage were significantly more common in hICC group. A total of 110 (75.3%) hICC patients and 119 (66.5%) HC patients experienced tumor recurrences, respectively. The median recurrence-free survival (RFS) and overall survival (OS) of hICC patients were significantly worse than those of HC patients (median RFS, 14.3 versus 22.7 months,  $P = 0.014$ ; median OS, 21.7 versus 30.6 months,  $P = 0.032$ ). Multivariate analysis revealed tumor size, satellite nodules, surgical margin, and histological grade as independent factors for OS in hICC patients. On the other hand, the presence of liver parenchyma invasion, portal invasion, lymphovascular invasion, later N stage, and positive surgical margin were associated with shorter OS in HC patients.

**Conclusions:** hICC showed distinct clinicopathological features, more aggressive biological behaviors, different prognostic factors, and worse prognosis in comparison with HC. Therefore, making a strict distinction between hICC and HC is necessary.

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## Introduction

Cholangiocarcinoma is a devastating malignancy originating from anywhere of the biliary epithelium [1]. According to the anatomic location along the biliary tree, cholangiocarcinoma is commonly divided into three distinct categories: intrahepatic, perihilar and distal cholangiocarcinoma [2]. These subsets are different in their epidemiology, clinical presentation, management, biologic features and patient outcomes.

Perihilar cholangiocarcinoma (PHC), which is defined as tumors arising predominantly at or near the biliary confluence distal to secondary branches of the right and left hepatic ducts and proximal to the cystic duct, is the most common type, accounting for about 50–70% of all cholangiocarcinoma [3,4]. However, due to the ill-defined boundary between extrahepatic and intrahepatic bile ducts, PHC potentially consists of two types of cholangiocarcinoma: “true” hilar cholangiocarcinoma (HC) and intrahepatic cholangiocarcinoma (IHC) involving the hepatic hilum (hICC). HC arises from the main lobar hilar bile ducts, while hICC arises from the segmental bile ducts with an intrahepatic component as well as invasion of the hepatic duct confluence. Previous studies suggested that both HC and hICC should be regarded as the same entity which

\* Corresponding author. Department of Bile Duct Surgery, West China Hospital of Sichuan University, No. 37 Guo Xue Xiang, Chengdu, 610041, Sichuan Province, China.

E-mail address: [nanshengcheng@163.com](mailto:nanshengcheng@163.com) (N.-S. Cheng).

can be grouped together by the term of “PHC”, considering their similar surgical procedures and similar features on image findings [5–7]. Other investigators, conversely, indicated that hICC might be excluded from PHC owing to its distinguishing biological behavior and worse prognosis [8–10]. Therefore, whether hICC and HC should be clinically clearly distinguished or combined remains highly controversial.

To our knowledge, few studies [6,8,10] have made a comparison between hICC and HC, especially in clinicopathological features, prognosis, and prognostic factors. Moreover, those published studies had limited numbers of resected hICC patients. Consequently, the aim of this study was to compare the clinicopathological characteristics and prognosis of hICC versus HC after curative-intent resection based on a large population of patients in a single center.

## Material and methods

### Patients selection

Between January 1998 and June 2015, a total of 325 consecutive patients with PHC (including hICC and HC) who underwent curative-intent resection at West China Hospital, Sichuan University were enrolled. We defined hICC as IHC (mass-forming type) involving the hilar bile duct, only if the center of the liver mass is located between the right side of the umbilical portion of the left portal vein and the left side of the right posterior portal vein [11]. The study exclusion criteria included patients who only underwent palliative resection (R2) or hilar bile duct resection, patients with gallbladder cancer involving hilar bile duct, patients with papillary and periductal infiltrating IHC involving hilar bile duct, patients who underwent re-resection after initial resection in another hospital. This study was approved by the Institutional Review Board of our hospital.

### Date collection and follow-up

Data on patient demographics, clinicopathological characteristics and operation-related variables were retrospectively collected. Overall survival (OS) was defined as the time from surgery to death of any cause or the last follow-up. Recurrence-free survival (RFS) was calculated from the date of surgery to the first documented recurrence, or last follow-up if alive without evidence of recurrence. All patients were strictly monitored and followed-up every 3–6 months. Adjuvant chemotherapy was not performed routinely, unless recommended by their attending physicians. The method used to calculate follow-up period was termed “reverse Kaplan-Meier”, which was the same calculation as “Kaplan-Meier”, except for the meaning of the status indicator reversed. Thus, censoring is an endpoint, and death censors the true but unknown observation time of an individual.

### Pathological assessment

The criteria used to distinguish between hICC and HC mainly depended on the location of tumor. HC was defined as cholangiocarcinoma mainly located at the hilar bile duct, while hICC was defined as cholangiocarcinoma predominantly located in the liver parenchyma with involvement of the adjacent hilar duct, and the center of the liver mass was located between the right side of the umbilical portion of the left portal vein and the left side of the right posterior portal vein. When it was difficult to identify the original tumor location, we would turn to pathologist and radiologists for help and reach a consensus. HC patients were staged according to the newly issued AJCC tumor node metastasis (TNM)

classification for PHC (eighth edition), whereas hICC patients were staged according to the TNM classification for IHC (eighth edition) [4].

### Statistical analysis

Numerical data were expressed as median (range). Differences between groups were compared using the Chi square test or Fisher's exact test for categorical variables and Mann–Whitney *U* test for numerical variables. The cumulative survival curves were analyzed using the Kaplan–Meier method, with the log-rank test being used for comparison. Univariate and multivariate Cox proportional hazard regression models were performed to determine potential prognostic factors for the RFS and OS. All statistical analyses were conducted using SPSS 21.0 software (IBM Corporation, Armonk, NY, USA), and a *p* value < 0.05 was considered statistically significant.

## Results

### Clinicopathological characteristics

Among the enrolled 325 consecutive patients with PHC, 146/179 patients were eventually diagnosed as hICC and HC, respectively. The patient demographic, clinicopathological characteristics and preoperative variables are summarized in Table 1. All the clinicopathological characteristics were comparable, except for portal vein invasion, tumor size, satellite nodules, adjacent organ invasion, and T staging. In our study, portal vein invasion, larger tumors, adjacent organ invasion and later T stage were significantly more common in the hICC group, when compared with the HC group.

### Surgical procedures and intraoperative variables

The surgical procedures and intraoperative variables are shown in Table 2. Left or right hemihepatectomy was the most frequent surgical procedure in both groups. Moreover, patients with hICC

**Table 1**  
Clinicopathological characteristics.

	hICC(n = 146)	HC(n = 179)	<i>P</i> value
Age (years) <sup>a</sup>	59(23–76)	61(31–78)	0.751
Sex			0.798
Male	82(56.2%)	98(54.7%)	
Female	64(43.8%)	81(45.3%)	
CA19-9 >200 U/ml	86(58.9)	91(50.8)	0.146
Preoperative PVE	9(6.2)	5(2.8)	0.137
Preoperative BD	67(45.9)	124(67.3)	<0.001
Tumor size (cm) <sup>a</sup>	3.9(1.6–10.1)	2.4(0.9–5.5)	<0.001
Portal vein invasion	54(37.0)	36(20.1)	0.001
Hepatic artery invasion	27(18.5)	29(16.2)	0.586
Perineural invasion	90(61.6)	98(54.7)	0.211
Lymphovascular invasion	23(15.8)	38(21.2)	0.209
Adjacent organ invasion	14(9.6)	6(3.4)	0.020
Lymph node metastasis	50(34.2)	57(31.8)	0.647
Satellite nodules	25(17.1)	3(1.7)	<0.001
R0 resection, n (%)	117(80.1)	147(82.1)	0.648
T stage			<0.001
1-2	78(53.4)	131(73.2)	
3-4	68(46.6)	48(26.8)	
Histological grade			0.198
Well differentiated	15	21	
Moderately differentiated	87	89	
Poorly differentiated	44	69	

Values in parentheses are percentages.

<sup>a</sup> Values are median (range); hICC, intrahepatic cholangiocarcinoma involving the hepatic hilum; HC, hilar cholangiocarcinoma; CA19-9, carbohydrate antigen 19–9; PVE, portal vein embolization; BD, biliary drainage.

**Table 2**  
Surgical procedures and intraoperative variables.

	hICC(n = 146)	HC(n = 179)	P value
Type of hepatectomy, n (%)			<0.001
Left hemihepatectomy	66(45.2)	62(34.6)	
Right hemihepatectomy	38(26.0)	39(21.8)	
Left trisectionectomy	18(12.3)	12(6.7)	
Right trisectionectomy	11(7.5)	7(3.9)	
Mesohepatectomy	8(5.5)	5(2.8)	
Parenchyma-preserving hepatectomy	5(3.4)	54(30.2)	
Hepatopancreatoduodenectomy, n (%)	4(2.2)	2(1.4)	0.279
Caudate lobectomy, n (%)	114(78.1)	148(82.6)	0.297
Portal vein resection, n (%)	39(26.7)	27(15.1)	0.010
Hepatic artery resection, n (%)	21(14.4)	16(8.9)	0.124
Operation time (min)	415(256–732)	397(268–965)	0.175
Intraoperative blood loss (ml)	557(202–3870)	494(160–3258)	0.773
Transfusion, n (%)	60(41.1)	66(36.9)	0.437
Postoperative morbidity, n (%)	58(39.7)	78(43.6)	0.484
Mortality, n (%)	6(4.1)	7(3.9)	0.927

hICC, intrahepatic cholangiocarcinoma involving the hepatic hilum; HC, hilar cholangiocarcinoma.

underwent more extensive hepatectomy, including left/right trisectionectomy, left/right hemihepatectomy. In contrast, parenchyma-preserving hepatectomy was more frequently performed in patients with HC. Compared with HC patients, patients with hICC had a higher incidence of portal vein resection. There were no significant differences in the intraoperative variables between HC and hICC patients. Postoperative morbidity was similar in both groups, mainly procedure-related complications (eg, bile leakage, liver failure). No statistically significant differences were found in postoperative 90-day mortality between the two groups.

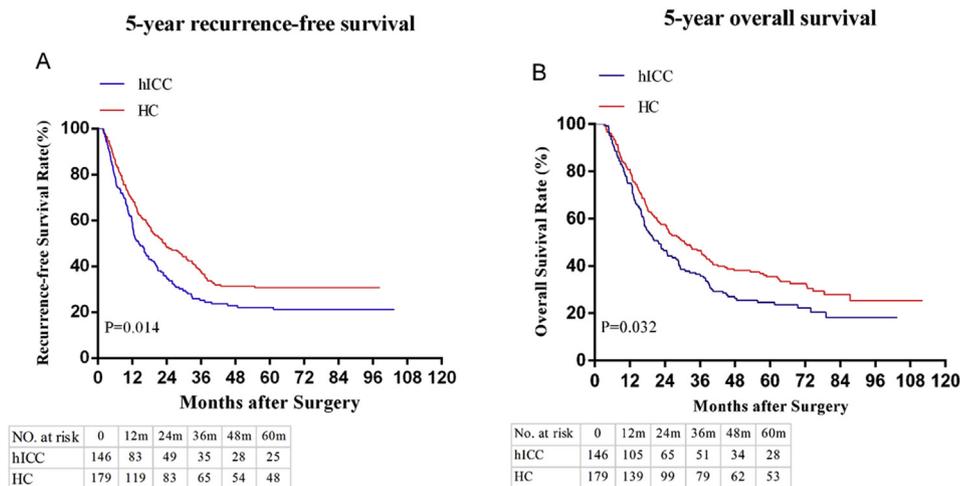
*Time to initial recurrence and recurrence site*

During the follow-up period (median duration was 72.7 months), 110 (75.3%) patients with hICC and 119 (66.5%) patients with HC experienced tumor recurrences, respectively. The median RFS of hICC patients was 14.3 months, which was significantly worse than that of HC patients (22.7 months) (Fig. 1A,  $P = 0.014$ ). The cumulative recurrence rates of hICC patients at 1, 3, and 5 years after curative-intent resection were 39.0, 70.5, and 78.8%, respectively, which were significantly lower than those of HC patients. More than half of the patients (55.9%) with hICC presented with

intrahepatic recurrence as their initial site, while liver recurrence was less common in patients with HC. Interestingly, the most common initial recurrence site for patients with HC was retroperitoneal lymph nodes (30.7%), followed by hepaticojejunostomy (21.4%) and peritoneum (18.5%).

*Prognostic factors for RFS*

In our univariate analysis, the presence of tumor size, portal vein invasion, hepatic artery invasion, lymphovascular invasion, satellite nodules, T stage, N stage, surgical margin, and histological grade were identified as predictors for RFS in patients with hICC (Supplemental Table 1). Multivariate analysis further demonstrated that only tumor size, portal vein invasion, lymphovascular invasion, satellite nodules, surgical margin, and histological grade significantly influenced RFS in patients with hICC (Supplemental Table 1). It's worth noting that, the variables independently correlated with shorter RFS in patients with HC were liver parenchyma invasion, lymphovascular invasion, N stage, and surgical margin (Supplemental Table 2).



**Fig. 1.** Comparison of recurrence-free survival (RFS) and overall survival (OS) between patients with intrahepatic cholangiocarcinoma involving the hepatic hilum (hICC) and hilar cholangiocarcinoma (HC) after curative-intent resection. A RFS of hICC patients was significantly shorter than that of HC patients ( $p = 0.014$ ). B OS of hICC patients was significantly shorter than that of HC patients ( $p = 0.032$ ).

### Survival

A total of 215 (66.1%) patients died of tumor recurrence during follow-up, and 81(24.9%) patients survived for more than 5 years. Seventy-one (21.8%) patients were currently alive without evidence of recurrence. The 1-, 3-, and 5-year OS rates of hICC patients were 71.9, 34.9, and 19.2%, respectively, with a median survival time of 21.7 months. When compared with hCC patients, HC patients had a remarkably better long-term survival after curative-intent resection (Fig. 1B,  $P=0.032$ ). Importantly, significant difference was found in survival rates between HC and hICC patients at each TNM stage (Supplemental Table 3).

### Prognostic factors for OS

Univariate analysis for OS indicated the same predictors as RFS in patients with hICC (Table 3). Our multivariate analysis further demonstrated only tumor size, satellite nodules, surgical margin, later N stage, and histological grade were independent factors for OS (Table 3). On the other hand, the presence of liver parenchyma invasion, portal invasion, lymphovascular invasion, later N stage, and positive surgical margin were identified by multivariate

analysis as independent predictors that contributed to shorter OS in patients with HC (Table 4).

### Discussion

Our results demonstrated that hICC was a more aggressive carcinoma with distinct biological features when compared with HC in respect to higher rates of recurrence, poorer survival, different prognostic factors and recurrence sites. In the present study, the clinicopathological characteristics were compared between hICC and HC, and we found that portal vein invasion, larger tumor size, satellite nodules, adjacent organ invasion and later T staging were significantly more frequent in hICC. Similar to our findings, Ebata et al. [6] reported that liver parenchyma invasion, portal vein invasion and lymph node metastasis were more common in hICC than in HC. This higher tendency might be attributed to the highly aggressive biological behaviors of hICC. Of note, when compared with HC, hICC was associated with larger tumor size and more satellite nodules, which were main high-risk factors for recurrence of IHC [12–14]. Therefore, our results indicated that hICC may exhibit different biological features from HC.

**Table 3**  
Univariate and multivariate analysis of OS for hICC patients who underwent liver resection.

	Univariate analysis				Multivariate analysis	
	No. Of patients	MST (months)	5-year OS (%)	<i>P</i>	HR (95% CI)	<i>P</i>
Age (years)						
<60	78	17.6	18.7	0.226		
>60	68	29.2	21.5			
Sex						
Male	82	17.2	19.0	0.452		
Female	64	28.5	21.3			
Biliary drainage						
Performed	67	24.7	21.5	0.344		
Not performed	79	17.8	18.7			
Tumor size (cm)						
<3	47	39.9	32.6	<0.001	1.652(1.035–2.638)	0.035
>3	99	16.9	13.8			
Portal vein invasion						
No	92	28.7	26.1	0.003	1.520(0.983–2.348)	0.060
Yes	54	16.0	9.6			
Hepatic artery invasion						
No	119	26.5	23.5	0.011	1.207(0.721–2.020)	0.474
Yes	27	15.8	4.0			
Perineural invasion						
No	56	23.5	26.4	0.112		
Yes	90	18.2	9.4			
Lymphovascular invasion						
No	123	22.7	22.9	0.040	1.182(0.677–2.065)	0.556
Yes	23	13.5	4.5			
Adjacent organ invasion						
No	132	22.6	19.7	0.453		
Yes	14	14.8	23.1			
Satellite nodules						
No	121	26.5	23.1	<0.001	1.907(1.076–3.379)	0.027
Yes	25	10.5	4.2			
T stage						
1-2	78	37.2	26	<0.001	1.448(0.940–2.232)	0.093
3-4	68	15.8	12.7			
N stage						
N0	96	29.4	27.2	<0.001	1.776(1.132–2.787)	0.012
N1	50	12.9	6.3			
Surgical margin						
Negative	117	28.9	25.0	<0.001	2.369(1.406–3.994)	0.001
Positive	29	12.5	0.0			
Histological grade						
Well-moderately differentiated	102	28.7	22.7	0.001	2.008(1.312–3.074)	0.001
Poorly differentiated	44	13.4	14.0			

OS, overall survival; hICC, intrahepatic cholangiocarcinoma involving the hepatic hilum; MST, median survival time; HR, hazard ratio; CI, confidence interval.

**Table 4**  
Univariate and multivariate analysis of OS for HC patients who underwent liver resection.

	No. Of patients	Univariate analysis			Multivariate analysis	
		MST (months)	5-year OS (%)	P	HR (95% CI)	P
Age (years)						
<60	89	33.3	34.1	0.558		
>60	90	26.4	27.6			
Sex						
Male	95	25.7	29.7	0.796		
Female	84	33.1	32.1			
Biliary drainage						
Performed	123	25.7	27.5	0.053		
Not performed	56	38.1	38.5			
Tumor size (cm)						
<3	121	32.6	32.2	0.348		
>3	58	24.2	27.8			
Depth of bile duct invasion						
Mucosal or fibromuscle layer	42	39.2	42.1	0.023	1.020(0.596–1.744)	0.942
Subserosal or peripheral adipose tissue	137	25.4	27.6			
Liver parenchyma invasion						
No	110	40.4	41.7	<0.001	2.098(1.400–3.145)	<0.001
Yes	69	17.2	12.5			
Portal vein invasion						
No	143	37.4	34.8	<0.001	1.972(1.039–3.744)	0.038
Yes	36	15.2	14.7			
Hepatic artery invasion						
No	150	33.1	33.1	0.190		
Yes	29	19.7	18.5			
Perineural invasion						
No	81	38.1	43.0	0.016	1.243(0.836–1.848)	0.283
Yes	98	25.4	20.4			
Lymphovascular invasion						
No	141	36.4	35.3	0.001	2.181(1.405–3.387)	<0.001
Yes	38	14.8	13.9			
Extent of liver resection						
Minor	59	28.1	25.0	0.354		
Major	120	30.8	33.3			
T stage						
1–2	131	37.4	36.2	0.003	1.285(0.696–2.372)	0.422
3–4	48	18.1	15.6			
N stage						
N0	122	40.4	41.7	<0.001	2.248(1.593–3.171)	<0.001
N1	51	17.1	9.8			
N2	6	11.2	0.0			
Surgical margin						
Negative	146	38.2	37.5	<0.001	2.495(1.560–3.990)	<0.001
Positive	33	16.1	0.0			
Tumor morphology						
Papillary	33	51.0	48.5	0.036	1.065(0.625–1.814)	0.818
Others	146	25.7	27.4			
Histological grade						
Well-moderately differentiated	110	36.7	35.2	0.038	1.173(0.790–1.742)	0.428
Poorly differentiated	69	19.3	23.4			

OS, overall survival; HC, hilar cholangiocarcinoma; MST, median survival time; HR, hazard ratio; CI, confidence interval.

Staging for hICC remains a difficult decision, particularly T staging. According to the newly issued AJCC cancer staging manual (eighth edition) [4], HC should be staged by the system for PHC. Undoubtedly, this classification is completely applicable for HC, however, it might be inappropriate for mass-forming hICC. The major determinants of the T classification of PHC are depth of bile duct invasion, liver parenchyma invasion, vascular invasion, which, yet, does not include key prognostic factors such as tumor size, satellite nodules, and adjacent organ invasion. In addition, we found that almost all the hICC involve the whole layer of bile duct combined with liver parenchyma invasion. Consequently, the staging system for HC might fail to well distinguish prognosis between T1 and T2 in hICC patients. What's more, hICC exhibit similar biological behaviors to IHC rather than HC. That was the reason why we decided to staging of hICC according to the TNM classification for IHC (eighth edition) in the present study. However, this staging of hICC did not take the invasion of secondary bile duct into

account. Thus, more appropriate staging of hICC should be proposed in the future.

With regard to the surgical procedures, extensive hepatectomy was performed more frequently in hICC patients, whereas parenchyma-preserving hepatectomy was more adopted in HC patients. This discrepancy might be attribute to the growth pattern of hICC and HC. hICC originally arises from unilateral segmental bile ducts and then invade the confluence, while HC directly originate from the confluence. Accordingly, obstructive jaundice developed relatively late in hICC patients when compared with HC patients, which may responsible for the more advanced stage of hICC at the time of initial diagnosis. That is why high rates of portal vein resection and major hepatectomy were performed in hICC patients. Consistent with previous studies [15–17], no significant difference in survival was found between the parenchyma-preserving hepatectomy group and major hepatectomy group in HC patients. Although parenchyma-preserving hepatectomy could also achieve

curative resection and similar surgical morbidity, it should be adopted in highly selected patients. Our evidence strongly suggested that extensive hepatectomy should be firstly considered in hICC patients, especially when combined with major vascular involvement.

Information about postoperative recurrence of hICC has been very limited to date. Zhang et al. [10] reported that the median RFS time of hICC patients was 13.0 months, which was significantly worse than 33.4 months of HC patients. In the current study, we reported the similar results, and we also found that the cumulative recurrence rates of hICC patients at 1, 3, and 5 years after curative-intent resection were significantly lower than those of HC patients. Surprisingly, unlike HC, the most common initial recurrence site for hICC was liver, rather than retroperitoneal lymph nodes. Interestingly, many studies confirmed that intrahepatic recurrence was predominant as an initial recurrence site in IHC [18–21]. These results indicate that hICC was a more aggressive tumor which present with early recurrence in liver, resembling IHC.

There has been dispute about the long-term survival between hICC and HC patients. Several studies reported that the OS of hICC patients was significantly worse than that of HC patients [6,8]. The authors pointed out, however, there was no significant difference in OS between hICC and HC patients when they were compared within the same TNM stage. Likewise, our results also demonstrated that hICC patients had a worse long-term survival than HC patients. In view of the different distribution of TNM stage among them, we compared their OS rates in the same TNM stage. In contrast with previous studies, significant difference was found in OS rates between HC and hICC patients in each stage.

Several prognostic factors for RFS and OS after curative-intent resection of HC has been reported, including portal vein invasion, lymphovascular invasion, lymph node metastasis, and surgical margin [22–25]. Our multivariate analysis also demonstrated the similar prognostic factors of HC as mentioned above, but when compared with hICC, there were no common statistically significant prognostic factors except for N stage and surgical margin. Actually, the prognostic factors of hICC in the present study, such as tumor size and satellite nodules, has been more commonly confirmed to be associated with the prognosis of IHC [12–14]. Thus, these findings again supported that hICC and HC seem to show distinct biological behaviors and prognosis.

Our results showed that the presence of portal vein invasion was an independent prognostic factor for RFS of hICC, yet it had no effect on OS ultimately. This inconsistency is likely to be related to the adoption of adjuvant chemotherapy after recurrence in these patients. Several recent studies indicated that adjuvant therapy could improve survival in resected PHC and IHC, especially for patients with lymph node metastasis and positive surgical margin [26–29]. These evidences strongly suggested effective adjuvant therapy should be considered in high-risk hICC and HC patients, even after curative-intent resection. In addition, a recent research indicate that neoadjuvant treatment might allow locally advanced PHC downstaging and improve tumor resectability, but with no effect on improving disease-free survival and OS [30]. However, another research showed that neoadjuvant treatment are required for “borderline resectable” HC with the presence of regional lymph node metastasis and vascular invasion to obtain better outcomes [31]. We also thought that some specific hICC and HC patients might benefit from neoadjuvant treatment, especially for those “borderline resectable” cases or patients requiring preoperative biliary drainage/portal vein embolization. Future large prospective randomized-controlled studies are needed to evaluate if this cohort of patients could really benefit from neoadjuvant and adjuvant therapy.

The present study has several limitations. The main limitation is its retrospective nature in a single center, but it is the largest series on recurrence and long-term survival after curative-intent resection of hICC. Another limitation is the unstandardized use of adjuvant chemotherapy, which may have impact on the results to some extent. In addition, although many clinicopathological variables related to prognosis were included in the survival analysis, some significant variables such as adjuvant chemotherapy were still lacked, which might affect the survival analysis.

In conclusion, hICC showed distinct clinicopathological features, more aggressive biological behaviors, different recurrence pattern, and worse prognosis in comparison with HC. Furthermore, their prognostic factors for RFS and OS were also largely different. Therefore, making a strict distinction between hICC and HC is necessary. Our results are clinically significant for establishment of treatment plan, as well as the prediction of prognosis in patients with hICC and HC.

### Conflicts of interest

The authors declare no conflict of interest.

### Declarations of interest

None.

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### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejso.2019.06.014>.

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