ORIGINAL ARTICLE

Intrahepatic Cholangiocarcinoma: Clinicopathological Differences Between Peripheral Type and Hilar Type

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Abstract

Background Intrahepatic cholangiocarcinoma (ICC) is categorized as peripheral ICC (PICC) or hilar ICC (HICC). The aims of this study are to clarify clinicopathological differences between PICC and HICC and to determine useful prognostic factors for patients with ICC following aggressive surgical resection.

Methods Medical records of 44 patients with ICC who underwent surgical resection were retrospectively reviewed. Clinicopathological factors were compared between patients with PICC and HICC. Univariate and multivariate models were used to analyze the effect of clinicopathological factors on disease-specific survival.

Results Disease-specific survival rates for the 44 patients were 76% at 1 year, 60% at 3 years, and 47% at 5 years. Clinicopathological factors did not differ between patients with PICC and HICC except preoperative jaundice ($P<0.001$), preoperative biliary drainage ($P=0.001$), postoperative complication ($P=0.046$), and macroscopic type ($P<0.001$). Multivariate analysis revealed that only lymph node status was an independent prognostic factor of disease-specific survival. The 5-year disease-specific survival rates of patients with or without nodal involvement were 23% and 66%, respectively ($P=0.004$).

Conclusions Clinicopathological characteristics are almost similar between patients with PICC and HICC. Nodal involvement is a potent prognostic factor for patients with ICC.

Introduction

Cholangiocarcinoma is usually divided into three categories based on location: intrahepatic tumors, which originate in the intrahepatic bile duct; perihilar tumors, which originate in the hepatic duct bifurcation; and distal tumors, which originate in the distal extrahepatic or intrapancreatic bile duct.[1] Of these three types, intrahepatic cholangiocarcinoma (ICC) represents approximately 10–20% of all cholangiocarcinomas.[1,2]

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The incidence and mortality rates of ICC are gradually increasing in Eastern and Western countries.[2–4]

Intrahepatic cholangiocarcinoma often involves the hepatic hilum, and therefore, ICC is generally divided into peripheral ICC (PICC) and hilar ICC (HICC).[5] Peripheral ICC requires hepatectomy alone and HICC requires hepatectomy with extrahepatic bile duct resection for surgical management. In previous reports on various aspects of ICC, most analyses included patients with both PICC and HICC,[6–29] while some investigators categorized cases of HICC into the perihilar cholangiocarcinoma group because they showed similar clinical features and required similar surgical procedures.[30–34] The differences in clinical features, pathological characteristics, and surgical outcome between PICC and HICC have not been fully elucidated.[22,27] Identification of the clinicopathological characteristics of patients with PICC and HICC is important to be able to plan a treatment strategy that includes appropriate surgical procedures and adjuvant therapy. The aims of this study are to clarify the clinicopathological differences between patients

with PICC and HICC and to determine useful prognostic factors for patients with ICC who have undergone aggressive surgical resection in a single institution.

Patients and Methods

Study Design

Medical records of 44 patients with ICC who were treated at the Department of Surgery, Hiroshima University Hospital between January 1995 and December 2010 were retrospectively reviewed. All patients underwent tumor resection with curative intent and had a confirmed pathological diagnosis.

For this study, ICC was defined as cholangiocarcinoma arising from the intrahepatic bile duct or bile ductules and located in the hepatic parenchyma. The tumors were classified as either PICC or HICC. Tumors classified as PICC were confined to the liver without involvement of the hepatic hilum and required hepatectomy alone, whereas tumors classified as HICC involved the hepatic duct confluence and required hepatectomy with extrahepatic bile duct resection (Fig. 1). All

Fig. 1 Macroscopic findings of peripheral intrahepatic cholangiocarcinoma (a) and hilar intrahepatic cholangiocarcinoma (b)

patients with HICC developed invasion of the bile duct in the hepatic hilum pathologically while all patients with PICC did not. Cases of cholangiocarcinoma arising from a bile duct confluence or from the first bifurcation were excluded, as were cases of intraductal ICC, or cases with combined hepatocellular and cholangiocarcinoma.

Eighteen clinicopathological factors, including patient demographics, perioperative factors, tumor characteristics, and patient survival, were compared between the two types of ICC. In addition, univariate and multivariate survival analyses were performed to determine useful prognostic factors of patients with ICC. Written informed consent was obtained from all patients for surgical treatment and pathological examinations according to the institutional guidelines.

Preoperative Workup and Surgical Procedures

Preoperative workup included ultrasonography, computed tomography, endoscopic ultrasonography, endoscopic retrograde cholangiography, and percutaneous transhepatic cholangiography to evaluate the local or distant tumor extensions. If jaundice was identified preoperatively, percutaneous transhepatic biliary drainage or endoscopic retrograde biliary drainage was performed to reduce the cholestatic liver damage. If the estimated liver resection volume exceeded 60% of the whole liver as calculated by computed tomography, then preoperative percutaneous transhepatic portal embolization was performed on the liver segment to be resected, in order to induce compensatory hypertrophy of the future remnant liver.

All surgical resections included hepatectomy with or without resection of the extrahepatic bile duct. Patients with PICC underwent hepatectomy alone while patients with HICC underwent hemihepatectomy or trisectionectomy with resection of the caudate lobe and extrahepatic bile duct. All patients underwent dissection of the regional lymph nodes, which included the nodes along the common hepatic artery, nodes in the hepatoduodenal ligament, and posterior pancreaticoduodenal nodes. Intraoperative pathological assessment of the distal bile duct transection lines was performed with frozen tissue sections. If the bile duct transection line was positive for malignant cells, further resection of the bile duct was performed to the maximum extent possible. When the extrahepatic bile duct was resected, biliary continuity was restored by a Roux-en-Y hepaticojejunal anastomosis.

Pathological Investigations

Following tumor resection, tumor size and macroscopic type were evaluated. The macroscopic type of ICC was determined based on the following three categories defined by the Liver
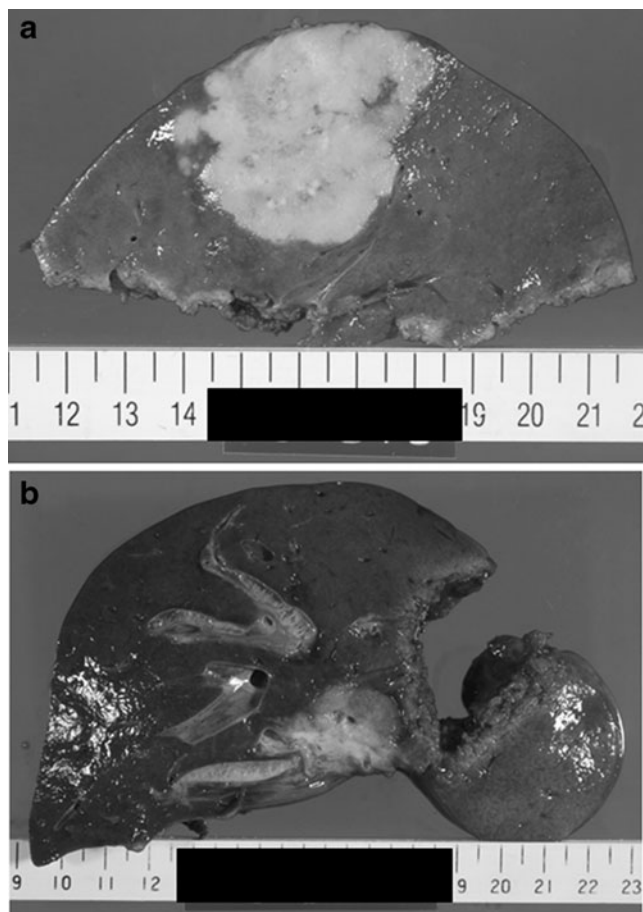
Cancer Study Group of Japan:[36] mass-forming (MF) type, periductal infiltrating (PI) type, and MF + PI type. Permanent sections with hematoxylin and eosin staining were prepared. All specimens were examined pathologically, and each tumor was classified as well-differentiated, moderately differentiated, or poorly differentiated adenocarcinoma according to the predominant pathological grading of differentiation. Presence of intrahepatic metastasis, serosal invasion, portal vein invasion, and lymph node metastasis were all pathologically examined. Intrahepatic metastasis, serosal invasion, portal vein invasion, and lymph node metastasis were defined pathologically in this study. Surgical margins were considered positive if infiltrating adenocarcinoma was present at the hepatic transection line, the distal bile duct transection line, or the dissected periductal soft tissue margins. The final stage of ICC was determined according to the TNM classification system of malignant tumors published by the International Union Against Cancer (UICC), 7th edition.[37]

Postoperative Adjuvant Chemotherapy

Beginning in 2002, postoperative adjuvant chemotherapy was routinely administered to patients with ICC, using a regimen that has been described previously.[6,11,38] In summary, patients were treated with 10 cycles of gemcitabine plus S-1 every 2 weeks. Each chemotherapy cycle consisted of intravenous gemcitabine at a dose of 700 mg/m^2 on day 1 and orally administered S-1 at a dose of 50 mg/m^2 for seven consecutive days, followed by a 1-week break from chemotherapy. Neither external beam radiation nor intraoperative irradiation was administered to any patient during the study period.

Survival

Patients were followed regularly in outpatient clinics at 3-month intervals by undergoing a blood test, ultrasonography, and computed tomography for up to 5 years after surgery. Information after 5 years was collected by telephone or personal interview. For patients who died, survival time after surgery and the cause of death were recorded. For surviving patients, postoperative survival time and status of recurrence were recorded. Only cancer-related deaths were considered as events and disease-specific survival was calculated. The median follow-up time after operation was 43 months (range, 1–196 months).

Statistical Analysis

The χ^2 test or Fisher exact test was used for comparison between the two groups. Survival curves were constructed using the Kaplan–Meier method, and differences in survival

curves were compared by univariate log-rank (Mantel–Cox) test. Factors found to be $P<0.05$ on univariate analysis were subjected to multivariate analysis using a Cox proportional hazards model. $P<0.05$ was considered statistically significant. Statistical analysis was performed with the Macintosh version of StatView version 5.0 (SAS Institute, Cary, NC, USA).

Results

Patient Demographics and Operative Procedures Performed

Of the 44 eligible patients, 25 had PICC and 19 had HICC. The patient group included 29 men (66%) and 15 women (34%) whose median age was 68 years (range, 37–81 years): 19 patients (43%) were more than 70 years old. Six patients (14%) were positive for hepatitis B virus (HBV) surface antigen or hepatitis C virus (HCV) antibody and eight patients (18%) had preoperative jaundice. For reduction of serum bilirubin levels or preoperative workup, percutaneous transhepatic biliary drainage was performed in seven (16%) patients and endoscopic retrograde biliary drainage in three (7%) patients. Percutaneous transhepatic portal embolization was performed in six patients (14%). Depending on the local extension of the tumor, a wide variety of hepatic resection procedures was performed. Major hepatectomy, including hemihepatectomy and trisectionectomy, was performed for 41 (93%) patients. All patients with HICC underwent caudate lobectomy and extrahepatic bile duct resection (Table 1). There was one perioperative death (2%) within 30 days of surgery. Postoperative complication occurred in 18 patients

Table 1 Operative procedures of patients with intrahepatic cholangiocarcinoma

	No. of patients	
	PICC (n=25)	HICC (n=19)
Right trisectionectomy + CHx + BDR		1
Left trisectionectomy + CHx + BDR		1
Right hepatectomy + CHx + BDR		7
Left hepatectomy + CHx + BDR		9
Central bisegmentectomy + CHx + BDR		1
Left trisectionectomy	1	
Right hepatectomy	8	
Left hepatectomy	12	
Central bisegmentectomy	1	
Segmentectomy	3	

HICC hilar intrahepatic cholangiocarcinoma, PICC peripheral intrahepatic cholangiocarcinoma, CHx caudate lobectomy, BDR bile duct resection

(41%). Biliary fistula was the most common complication (*n*=9), followed by intraabdominal abscess (*n*=3), chylous ascites (*n*=2), and miscellaneous complications (*n*=4). Postoperative adjuvant chemotherapy was performed for 23 patients (52%).

Tumor Characteristics

Mean tumor size was 45.8 mm (range, 15–140 mm). The macroscopic categories of the tumors were 17 (39%) of MF type, 9 (20%) of PI type, and 18 (41%) of MF + PI type. Tumors were pathologically identified as well-differentiated adenocarcinoma in 15 patients (34%), moderately differentiated adenocarcinoma in 18 patients (41%), and poorly differentiated adenocarcinoma in 11 patients (25%). Intrahepatic metastasis, serosal invasion, and portal vein invasion were identified in 10 (23%), 10 (23%), and 20 patients (45%), respectively. There were 20 tumors (45%) with lymph node metastasis and 24 (55%) without lymph node metastasis. Twenty-seven patients (61%) had negative surgical margins. According to the UICC staging system, 10 (23%), 10 (23%), 5 (11%), and 19 patients (43%) had pT1, pT2a, pT2b, and pT3 tumors, respectively, and 8 (18%), 9 (20%), 7 (16%), 17 (39%), and 3 patients (7%) were diagnosed with stage I, II, III, IVA, and IVB disease, respectively.

Comparison of Clinicopathological Factors Between PICC and HICC

Table 2 compares several clinicopathological factors between patients with PICC and HICC. No significant difference was found between the two groups in terms of gender, age, HBV or HCV infection, use of percutaneous transhepatic portal embolization, type of hepatic resection, use of adjuvant chemotherapy, tumor size, tumor differentiation, intrahepatic metastasis, serosal invasion, portal vein invasion, lymph node status, surgical margin status, UICC pT factor, or UICC stage. However, the rates of preoperative jaundice (*P*<0.001), preoperative biliary drainage (*P*=0.001), postoperative complication (*P*=0.046), and PI or PI+MF type (*P*<0.001) were significantly lower in patients with PICC than in patients with HICC (Table 2). Disease-specific survival was not different between patients with PICC and HICC (Fig. 2): the 5-year disease-specific survival rates of patients with PICC and HICC were 59% and 35%, respectively (*P*=0.560, Fig. 2).

Prognostic Factors of Patients with ICC

Overall survival rates for the 44 patients were 78% at 1 year, 52% at 3 years, and 31% at 5 years, and disease-specific survival rates were 76% at 1 year, 60% at 3 years,

Table 2 Clinicopathological characteristics of patients with hilar and peripheral intrahepatic cholangiocarcinomas

	No. of patients		*P* value
Gender	PICC (*n*=25)	HICC (*n*=19)	
Male	13	16	0.052
Female	12	3	
Age (years)			
<70	16	9	0.270
≧70	9	10	
Hepatitis B infection			
Yes	2	0	0.498
No	23	19	
Hepatitis C infection			
Yes	4	1	0.370
No	21	18	
Preoperative jaundice			
Yes	0	8	<0.001
No	25	11	
Preoperative biliary drainage			
Yes	1	9	0.001
No	24	10	
Preoperative portal vein embolization			
Yes	2	4	0.378
No	23	15	
Hepatectomy			
Left side	13	10	0.967
Right side	12	9	
Postoperative complication			
Yes	7	11	0.046
No	18	8	
Adjuvant chemotherapy			
Yes	13	10	0.967
No	12	9	
Macroscopic type			
MF	16	1	<0.001
PI, MF + PI	9	18	
Tumor size (mm)			
<45	12	14	0.125
≧45	13	5	
Tumor differentiation			
Well	8	7	0.737
Moderate, poor	17	12	
Intrahepatic metastasis			
Yes	7	3	0.474
No	18	16	
Serosal invasion			
Yes	7	3	0.680
No	18	16	
Portal vein invasion			
Yes	13	7	0.317
No	12	12	

Table 2 (continued)

	No. of patients		P value
Lymph node metastasis			
Yes	10	10	0.405
No	15	9	
Surgical margin			
Positive	9	8	0.680
Negative	16	11	
UICC pT factor			
pT1, 2	16	9	0.270
pT3	9	10	
UICC stage			
I, II	11	6	0.402
III, IV	14	13	

HICC hilar intrahepatic cholangiocarcinoma, *PICC* peripheral intrahepatic cholangiocarcinoma, *MF* mass-forming type, *PI* periductal infiltrating type, *UICC* International Union Against Cancer

and 47% at 5 years. The median survival time was 27.8 months (range, 1–196 months). Tumor recurrence occurred in 22 patients. The sites and nature of recurrence in these patients included peritoneal dissemination ($n=14$), liver metastases ($n=4$), local disease ($n=3$), and lung metastasis ($n=1$). Nineteen patients died of recurrent disease, and five patients died of other diseases. Two patients with liver metastasis and one patient with local recurrence were still alive at the time of this writing.

Eighteen clinicopathological factors were investigated using the log-rank test to determine their prognostic significance. Gender, age, type of ICC, HBV or HCV
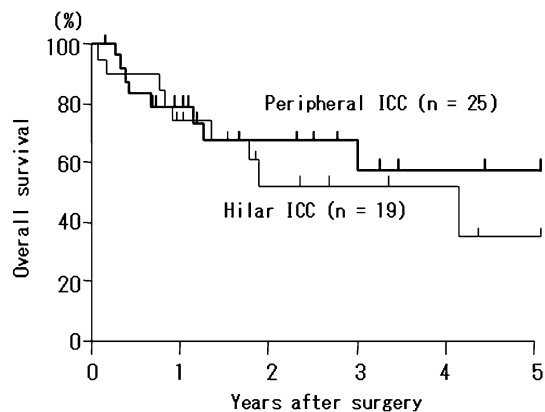
Fig. 2 Comparison of disease-specific survival between patients with peripheral intrahepatic cholangiocarcinoma and those with hilar intrahepatic cholangiocarcinoma ($P=0.560$). *ICC* intrahepatic cholangiocarcinoma

Table 3 Univariate and multivariate survival analyses of prognostic factors for patients with intrahepatic cholangiocarcinoma

Factors	Univariate analysis			Multivariate analysis	
	No. of patients	5-year survival rate (%)	P value	Hazard ratio (95% CI)	P value
Gender					
Male	29	49	0.469		
Female	15	48			
Age (years)					
<70	25	51	0.645		
≧70	19	44			
Type of intrahepatic cholangiocarcinoma					
Hilar	19	35	0.560		
Peripheral	25	59			
Hepatitis B infection					
Yes	2	0	0.991		
No	42	48			
Hepatitis C infection					
Yes	5	0	0.915		
No	39	47			
Preoperative jaundice					
Yes	8	0	0.371		
No	36	57			
Preoperative biliary drainage					
Yes	10	0	0.393		
No	34	57			
Preoperative portal vein embolization					
Yes	6	0	0.814		
No	38	47			
Hepatic resection					
Left side	23	47	0.701		
Right side	21	54			
Postoperative complication					
Yes	18	36	0.407		
No	26	58			
Adjuvant chemotherapy					
Yes	23	0	0.104		
No	21	33			
Macroscopic type					
MF	17	20	0.892		
PI, MF + PI	27	38			
Tumor size (mm)					
<45	26	33	0.629		
≧45	18	0			
Tumor differentiation					
Well	15	66	0.202		
Moderate, poor	29	37			
Intrahepatic metastasis					
Yes	10	40	0.459		

Table 3 (continued)

Factors	Univariate analysis			Multivariate analysis	
	No. of patients	5-year survival rate (%)	P value	Hazard ratio (95% CI)	P value
No	34	51			
Serosal invasion					
Yes	17	30	0.095		
No	27	58			
Portal vein invasion					
Yes	20	0	0.022	2.10	0.158
No	24	60		(0.75–5.88)	
Lymph node metastasis					
Yes	20	23	0.004	3.21	0.032
No	24	66		(1.10–9.33)	
Surgical margin					
Positive	17	35	0.128		
Negative	27	39			
UICC pT factor					
pT1, 2	25	59	0.121		
pT3	19	33			
UICC stage					
I, II	17	69	0.022		
III, IV	27	33			

MF mass-forming type, *PI* periductal infiltrating type, *CI* confidence interval, *UICC* International Union Against Cancer
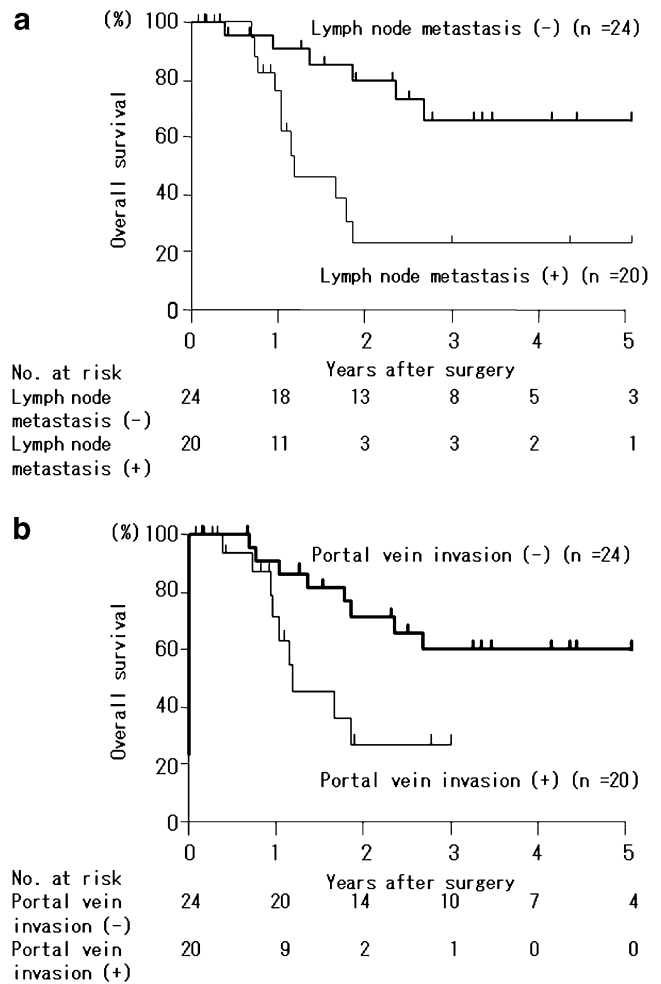
Fig. 3 Comparison of disease-specific survival of patients with intrahepatic cholangiocarcinoma. Stratified by the presence or absence of nodal involvement (**a**, *P*=0.004). Stratified by the presence or absence of portal vein invasion (**b**, *P*=0.022)

infection, preoperative jaundice, preoperative biliary drainage, use of percutaneous transhepatic portal embolization, type of hepatic resection, use of adjuvant chemotherapy, macroscopic type, tumor size, tumor differentiation, intrahepatic metastasis, serosal invasion, surgical margin status, and UICC pT factor did not influence postoperative disease-specific survival by univariate survival analysis. In contrast, univariate analysis revealed that portal vein invasion (*P*=0.022), lymph node status (*P*=0.004), and UICC stage (*P*=0.006) were significantly associated with disease-specific survival. These factors were entered into multivariate analysis with a Cox proportional hazards model, and only lymph node metastasis (*P*=0.032) remained independently associated with disease-specific survival. UICC stage was not used as a dependent variable in multivariate survival analysis to avoid confounding with nodal status (Table 3). The 5-year disease-specific survival rates of patients with or without lymph node metastasis were 23% and 66%, respectively (*P*=0.004, Fig. 3a). The 5-year disease-specific survival rates of patients with or without portal vein invasion were 0% and 60%, respectively (*P*=0.022, Fig. 3b).

Discussion

In the current study, we focused on identifying clinicopathological and outcome differences between patients with PICC and those with HICC. We found that the rates of preoperative jaundice, preoperative biliary drainage, PI or PI + MF type, and postoperative complication in patients with PICC were lower than those in patients with HICC. These results are reasonable because HICC involves the hepatic hilum and requires resection of the extrahepatic bile duct and hepaticoenteric anastomosis for surgical treatment. However, other clinicopathological factors, including lymph node metastasis, vascular invasion, and UICC stage, did not differ between the two groups.

A few other comparative studies on clinicopathological differences between patients with PICC and HICC have been published. Nakagohri et al.[27] reported that in contrast with our findings, lymph node status and margin status

were different between PICC and HICC, and that HICC was the more aggressive disease in a retrospective review of 40 patients with ICC. In addition, Aishima et al.[22] reported that in an analysis of 53 patients with ICC, lower frequency of lymph node metastasis was found in patients with PICC compared with those with HICC. One potential reason for the difference in results between this study and previous reports might be the disparity of HBV or HCV infection in the patient populations. Patients with HBV or HCV infection reportedly have more indolent tumors than do patients without HBV or HCV infection.[9,39] Zhou et al.[39] reported that the rate of lymph node metastasis in ICC patients with HBV infection was significantly lower than that in ICC patients without HBV infection. Hepatitis B virus or HCV infection in this series and in Aishima's series was found in 20% and 47% of patients with PICC, respectively, which might explain the more aggressive features of PICC in the current study.

Several investigators have compared the 5-year survival rate of patients with PICC with that of patients with HICC. According to these reports, some investigators reported that

the 5-year survival rate of patients with PICC was significantly higher than that of patients with HICC,[11,14,20–22,25] although others reported that the 5-year survival rates between the two groups did not differ.[7,12,15,18,27,35] Aishima et al.[20] reported that the disease-specific 5-year survival rate of patients with PICC was significantly better than that of patients with HICC (60% vs. 36%, $P=0.012$). Guglielmi et al.[11] reported that among 52 patients with ICC, patients with PICC had a better overall 5-year survival rate than those with HICC (26% vs. 0%, $P=0.02$). In contrast, Lang et al.[14] mentioned that there was no significant difference in recurrence-free survival between patients with PICC and HICC in an analysis of 53 patients with ICC. However, these reports were based on a small number of patients. Uchiyama et al.[35] analyzed 341 patients with ICC who underwent surgical resection at nine Japanese high-volume centers and found no significant difference in overall 5-year survival rate between patients with PICC and HICC (overall 5-year survival rate, 26% vs. 33%, $P=0.090$). In the current study, no significant difference was seen in disease-specific survival between patients with PICC and HICC. Further studies on a

Table 4 Recent reports on resectional treatment of intrahepatic cholangiocarcinoma

Author	Year	No. of patients	Mortality (%)	Curative resectability (%)	Nodal involvement (%)	Median survival (months)	5-year survival rate (%)	Prognostic factors by multivariate analysis
Present study	2011	44	2	61	45	28	31	N
Uchiyama[35]	2010	341	3	80	50	20	29	N, CA19-9, IM, R
Cho[10]	2010	63	2	94	30	–	32	Age, CA19-9, LI, R
Zhang[9]	2010	40	0	75	28	25	28	TS, N
Saxena[8]	2010	40	2	70	28	33	28	CA19-9, G, N
Ercolani[7]	2010	64	0	83	29	57	48	Year of operation
Shirabe[30]	2010	60	0	72	43	–	31	G, LI
Guglielmi[13]	2009	52	4	83	27	40	20	N, VI
Lang[14]	2009	83	7	64	34	26	21	Sex, R
Yedibela[15]	2009	45	4	80	13	37	35	N, R, BL, BT
Choi[34]	2009	64	2	86	27	39	40	G
Nakagohri[16]	2008	56	9	75	38	22	32	IM
Shirai[17]	2008	59	12	85	54	–	–	N, G, IM, PNI
Tamandl[18]	2008	74	10	80	31	31	28	TS, IM
Uenishi[19]	2008	133	–	83	47	18	29	N, IM, R
Endo[20]	2008	82	1	85	9	36	–	N, IM, TS
Shimada[12]	2007	74	1	69	46	24	31	IM, MT
Miwa[23]	2006	41	0	76	39	–	29	–
Nakagawa[24]	2005	44	6	75	46	24	31	IM, R
Tajima[25]	2004	35	11	61	65	–	25	PNI, R, IDPCC
Morimoto[26]	2003	51	4	67	33	–	32	R, N, TS, MT
Ohtsuka[28]	2002	48	8	–	39	26	23	IM, CA19-9
Weber[29]	2001	33	3	88	15	37	31	VI

N nodal involvement, *CA19-9* serum carbohydrate 19-9 level, *IM* intrahepatic metastasis, *R* pathologically curative resection, *LI* lymphatic invasion, *TS* tumor size, *G* pathological grading of differentiation, *VI* vascular invasion, *BL* blood loss, *BT* blood transfusion, *PNI* perineural invasion, *MT* macroscopic type, *IDPCC* intraductal papillary carcinoma component

larger number of patients are needed to clarify a survival difference between patients with PICC and HICC.

Many investigators have used multivariate analysis to determine useful prognostic factors for ICC after surgical resection (Table 4).[7–10,12–20,23–26,28–30,34,35] According to these reports, potentially significant factors include intra-hepatic metastasis,[12,16,17,19,20,24,28,35] serum carbohydrate antigen 19-9 level,[8,35] pathological grading of differentia-tion,[8,17,30] vascular invasion,[13,29] tumor size,[9,18,20] and pathologically curative resection.[10,14,15,19,24–26,35] In addi-tion, lymph node metastasis was reported to be one of the most significant independent prognostic factors for patients with ICC by multivariate survival analysis.[8,9,13,15,17,19,20,26,35] In the current study, the disease-specific survival of patients with nodal involvement was significantly worse than that of patients without nodal involvement, and multivariate analy-sis revealed that only lymph node status was an independent prognostic factor for patients with ICC.

The reported frequency of nodal involvement in patients with ICC who underwent surgical resection ranges from 6% to 65% (Table 4).[7–10,12–20,23–26,28–30,34,35] Frequency of nodal involvement in the current study was comparable to that of previous reports, at 45% of patients. However, previously published 5-year survival rates for patients with lymph node metastasis differ substantially from those in the current study. Several investigators reported that no patients with nodal involvement had survived for more than 5 years,[7,9,15,16,23,30] and others reported a 5-year survival rate that ranged from 6% to 17%.[13,14,17,19,22,25,26,29] A multicenter analysis conducted by the Study Group for Hepatic Surgery of the Japanese Society of Hepato-Biliary-Pancreatic Surgery[35] showed that of 139 patients with ICC who had lymph node involvement, only seven patients survived for more than 4 years, and three patients survived for more than 5 years: the 5-year survival rate was 7%. Based on these results, some investigators reported that radical resection should be contraindicated for patients with nodal involvement,[40] or that lymph node dissection might not improve survival of patients with ICC.[41] However, in the current study, two patients with nodal involvement have survived for more than 4 years without recurrence[42] and the overall 5-year survival rate of patients with nodal involve-ment was 21%, which was an excellent result compared with that of previous reports. In our institution, dissection of the regional lymph nodes is routinely performed for all patients with ICC. We believe that routine lymph node dissection may contribute to a relatively favorable progno-sis for patients with nodal involvement.[7]

We have already reported the prognostic impact of adjuvant chemotherapy for patients with biliary carcinoma in the recent reports.[6,11,38,43] However, we could not demonstrate a beneficial effect of adjuvant chemotherapy for patients with ICC in this study. The reasons for this result are probably that this study was based on a small number of patients and follow-up time of patients was short. However, survival of patients who received adjuvant chemotherapy tended to be better than that of patients who did not (3-year disease-specific survival rate, 63% vs. 33%). Further studies on a larger number of patients with long-term follow-up are needed to confirm the prognostic impact of adjuvant chemotherapy for patients with ICC.

In conclusion, the clinicopathological characteristics of patients with PICC were almost similar to those of patients with HICC, and long-term outcome was similar between the two groups. Lymph node status was a potent prognostic factor for patients with ICC. However, the limitations of this study are its retrospective design and the small number of patients studied. Further studies on larger numbers of patients are required to confirm the results of this study.

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