

Optimal extent and role of LN dissection for Intrahepatic Cholangiocarcinoma

Kazuhisa Uchiyama

Osaka Medical College, Japan

Aim

In Intrahepatic Cholangiocarcinoma (ICC) patients, several clinicopathological factors such as tumor markers, macroscopic type, tumor size, tumor number, histological differentiation status, surgical margins, and lymph node metastasis, have been reported to be significant prognostic factors for survival. However, it still remains controversial as to whether ICC patients with lymph node metastasis can obtain any survival benefit from surgery. Lymph node dissection for ICC remains a controversial issue. Although it has been suggested that the standard surgical procedure for ICC is hepatectomy combined with extensive nodal dissection, some centers do not support routine application of lymph node dissection. Selective lymphadenectomy and limited application of lymph node dissection⁸ has been reported for other institutions. In other words, only suspicious lymph nodes were submitted for frozen section examination before proceeding to liver resection in these cases, whereas other authors advocate lymph node dissection only in the context of extended resection and not as far as standard resection is concerned. There is currently no evidence concerning the efficacy of extended lymphadenectomy in ICC patients. By the retrospective consecutive analysis of the 9 high-volume centers, we investigated the outcomes of ICC patients with lymph node metastasis following hepatic resection, and analyzed the prognostic factors affecting patient survival. The distribution of the lymph node metastases and the influence of the extent of lymph node dissection on survival were examined in order to clarify the indications for the surgical treatment of ICC with lymph node metastases. The aim of this study was to clarify the prognostic factors of ICC following hepatectomy and to examine the impact of lymph node metastasis on survival. This study was therefore carried out as a Project Study of the Japanese Society of Hepato-Biliary-Pancreatic Surgery.

Patients and Methods:

Three hundred and forty-one consecutive patients with ICC who underwent hepatectomy between 1995 and 2004 at the 9 institutions of the Medical University Hospitals were retrospectively analyzed. These 9 institutions selected for this project study are high-volume centers in Japan, and in these centers, the standard procedure for ICC is hepatectomy combined with dissection of primary lymph nodes. ICC was defined as adenocarcinoma arising from the second order or more distal branches of the intrahepatic bile ducts. Patients with combined

hepatocellular carcinoma and cholangiocarcinoma or bile duct cystadenocarcinoma were excluded from this study cohort. The patient demographics, medical history, symptoms, laboratory findings, clinicopathological features, surgical management, and hospital morbidity and mortality were reviewed. All patients underwent routine liver function tests: bilirubin, albumin, prothrombin time, alkaline phosphatase, transaminase, hepatitis B surface antigen (HBsAg), antibody to hepatitis C virus (anti-HCV) and indocyanine green test, and their blood cells counts, serum creatinine levels, serum carcinoembryonal antigen (CEA) and carbohydrate antigen (CA) 19-9 assays, and the results of chest radiography before hepatectomy were all examined. The pre-operative diagnosis was based on a combination of imaging data including computed tomography (CT), ultrasonography (US) and/or magnetic resonance imaging (MRI).

Lymph node dissection was not performed uniformly in all patients because of the multi-center retrospective nature of the study. Of the 341 patients, 111 patients did not undergo lymph node dissection (68 patients) or lymph node sampling along the hepatoduodenal ligament lymph nodes (43 patients), and they did not demonstrate lymph node metastases in the preoperative imaging studies. Our lymph node sampling indicates that only suspicious lymph nodes were submitted for frozen section examinations. The lymph nodes were retrieved in 228 patients with extended lymph node dissection which means the lymphadenectomy beyond the hepatoduodenal ligament nodes, including lymph nodes along the common hepatic artery and retropancreas and/or more distal lymph nodes.

Macroscopically, the number of tumors, tumor size, macroscopic type, and surgical margins of the tumors were evaluated. The macroscopic type of ICC was categorized into the following types: mass forming (MF), periductal infiltration (PI), and intraductal growth (IG) types, according to the Liver Cancer Study Group of Japan. The microscopic characteristics evaluated were: histological type, level of differentiation, margin status, and the presence of lymph node metastases. We categorized the distribution of lymph node metastases as: hepatoduodenal ligament lymph nodes (n1), lymph nodes along the common hepatic artery and retropancreatic lymph nodes (n2), lymph nodes along the celiac axis and left gastric artery (n3), and para-aortic lymph nodes (n4).

Hepatectomy was defined as the resection of one or more liver segments by Couinaud's definition. After resection, all patients underwent regular follow-ups over a 5-year period (or until death) with clinical examinations and blood chemistry evaluations. The patients were screened for CEA and CA19-9 to identify tumor recurrence after operation, and underwent a CT scan and/or MRI. Adjuvant chemotherapy with various protocols, usually based on 5-FU, cisplatin, or gemcitabine without tumor relapse after surgery, was performed in only 68 of the 341 patients. Survival was calculated in terms of the resection margin, tumor nodules, tumor size, status of the lymph node metastasis, blood loss, periductal invasion, tumor differentiation, biliary tract reconstruction, and lymph node dissection and adjuvant chemotherapy following the operation. The width of the resection margin was measured in patients with an R0- resection. Disease-free survival was calculated from the date of surgery to the date of recurrence, and the overall survival was calculated from the date of surgery.

Results

Background of patients and preoperative clinical findings

The demographic and preoperative clinical data of 341 patients who underwent liver resection with ICC are shown in Table 1. There were 217 male and 124 female patients, with a mean age of 64 years (range: 30 to 84 years). Causes of liver disease were hepatitis B virus in 32 patients (9.4%) and hepatitis C virus in 64 patients (18.8%). Among the 341 patients who underwent a liver resection, the MF type was present in 183 (54%), PI+ MF type in 100 (29%), PI type in 29 (9%), and IG type in 22 (7%) patients. The tumor was identified as a well-differentiated adenocarcinoma in 56 patients (21%), moderately differentiated type in 177 (66%), and poorly differentiated type in 37 (14%). Preoperative abnormal blood chemical data of the median values were found in serum CA19-9 (135U/ml, range: 0.1 to 120,000 u/ml) and serum alkaline phosphatase (401 IU/L, range: 25 to 5,335 IU/L) (Table 2).

Hepatectomy procedures and intraoperative findings

Tumor removal was achieved by right hepatectomy in 90 patients, right trisectionectomy in 18, left hepatectomy in 118, left trisectionectomy in 25, central hepatectomy (ie, Couinaud segments 4, 5 and 8) in 10, right anterior sectionectomy in 7, right posterior sectionectomy in 9, left lateral sectionectomy in 15, segmentectomy in 14, and nonanatomic liver resection in 21 patients (Table 3). There were 261 extended resections (>2 liver sections; 76.5% of the 341 patients). The associated biliary procedures included resection of the biliary confluence and extrahepatic bile duct with Roux-en-Y hepatico-jejunostomy in 195 patients (57.1%) and vascular reconstructions were required in 53 patients (15.5%). Vascular reconstruction consisted of portal vein anastomosis in 29 patients, hepatic artery anastomosis in 5 pa-

Table 1. Background of the patients (1995-2004, n=341)

Age (years)*	64 (30-84)
Gender (Male / Female)	217 / 124
Child-Pugh class	
A / B / C	261 / 28 / 0
Background liver	
Normal / Chronic hepatitis / Cirrhosis	213 / 48 / 28
Viral infection	
B / C / B and C / no viral infection	23 / 55 / 9 / 254
History of blood transfusion	
Yes / No	25 / 236
Macroscopic tumor type **	
MF / PI+MF / PI / IG	190 / 100 / 29 / 22
Histological differentiation type	
Well / Moderate / Poorly	56 / 177 / 37

*Values are expressed as the median (range).

**MF: mass forming type, PI: periductal infiltrating type, IG (intraductal growth type)

Table 2. Preoperative blood chemical data (1995-2004, n=341)

Total bilirubin (mg/dl)	0.7 (0.1-22.7)
Albumine (mg/dl)	3.9 (2.5-5.2)
ICG test (%)*	9.6 (1.0-39.0)
Prothrombin time (%)	94 (33-150)
CA19-9 (u/ml) **	135 (0.1-120,000)
CEA (ng/ml)***	3.3 (0.6-3,570)
AST (IU/L) #	33 (9-287)
ALT (IU/L) ##	31 (6-624)
Alkaline phosphatase (IU/L)	401 (25-5,335)
Platelet (10 ⁴ /μl)	22 (6-57)

Values are expressed as the median (range).

ICG test; indocyanine green test

CA 19-9; carbohydrate antigen 19-9

CEA; carcinoembryonic antigen

AST; aspartate aminotransferase

ALT; alanine aminotransferase

tients, and inferior vena cava anastomosis (including the hepatic vein) in 19 patients because of the possibility of a curative liver resection for ICC. The median blood loss was 1,400 ml (range: 50 to 10,350 ml) and the median duration of surgery was 435 minutes (range: 90 to 1,140 min). Regarding to the tumor findings during

Table 3. Hepatectomy procedures

	Resected sub-segment (Couinaud's classification)	number	subtotal
Hemi-hepatectomy or more			261 (76.5%)
Right hepatectomy **	5,6,7,8	90	
Right tri-sectionectomy	4,5,6,7,8	18	
Left hepatectomy **	2,3,4	118	
Left tri-sectionectomy	2,3,4,5,8	25	
Central hepatectomy	4,5,8	10	
Sectionectomy			31 (9.1%)
Right anterior sectionectomy	5,8	7	
Right posterior sectionectomy	6,7	9	
Left lateral sectionectomy	2,3	15	
Segmentectomy			14
Partial resection			21
Others ***			14
total			341

Biliary tract reconstructions were conducted in 195 patients and vascular reconstructions were required in 53 patients

* Including extended hepatectomy

** The cases with multiple liver resections for multi-focal tumors

Table 4. Operative Morbidity and Mortality

Complication	number (%)
Bile leakage	44 (12.9%)
Surgical site infection	42 (12.3%)
Pleural effusion	30 (8.8%)
Intra-abdominal fluid collection	18 (5.3%)
Hyper bilirubinemia	16 (4.7%)
Liver failure	13 (3.8%)
Intra-abdominal bleeding	7 (2.1%)
Gastrointestinal bleeding	6 (1.8%)
Pneumonia	2 (0.6%)
Others	2 (0.6%)

All complication	191
Postoperative death	11 (3.2%)

Complication rate; 128/341(37.5%)

surgery, the median tumor diameter (in the case of multifocal tumors, the diameter of largest nodule) was 45 mm (range: 7 to 180 mm), and solitary tumors were found in 242 patients (70.9%).

Postoperative mortality and morbidity

Postoperative mortality (within 30 days or during the initial hospitalization) occurred in 11 of the resected patients (3.2%). A total of 117 cases of postoperative morbidity occurred in the 341 patients (34.3%), including bile leakage (n=44), surgical site infection (n=42), pleural effusion (n=30), intra-abdominal fluid collection (n=18), hyper-bilirubinemia (n=16), and liver failure (n=13) (Table 4). None of the complications correlated with either the type of liver resection or the extension of the resection to include major vessels and/or adjacent structures, nor was there any direct correlation with the extent of lymph node metastasis. The median hospitalization period was 29 days (range: 5 to 744 days).

Survival and prognostic factors

All patients were followed for over 5 years (range; 5.0-10.5 years). The overall median survival was 20.0 months, with cumulative 3- and 5-year rates of 36.4 and 29.2%, respectively. A total of 75 patients (21.7%) survived more than 5 years. The median recurrence-free survival was 10.1 months, with 3- and 5-year rates of 29.5

Table 5. Univariate and multivariate analysis of prognostic factors on overall survival following hepatectomy

Variables	number	Univariate analysis			Multivariate analysis			
		Survival (%)		p Value**	hazard ratio	95% C.I.	p Value *	
		3year	5year					
Gender	Male	217	34.7	26.9	0.257			
	Female	124	39.5	33.1				
Liver cirrhosis	no	310	36.8	29.0	0.431			
	yes	13	48.4	48.4				
Serum CA 19-9 (U/ml)	≤135	158	59.1	50.9	<0.001	2.07	1.41-3.05	<0.001
	>135	154	21.3	13.3				
Tumor size (cm)	≤5cm	204	42.9	35.9	<0.001	1.11	0.79-1.54	0.566
	>5cm	130	25.1	17.2				
The number of tumors	single	242	43.9	36.4	<0.001	2.00	1.39- 2.90	<0.001
	multiple	97	17.5	9.2				
Pathological lymph node metastasis	negative	141	52.9	46.4	<0.001	2.10	1.41- 3.00	<0.001
	positive	139	13.6	7.0				
Blood loss (ml)	≤ 1,400	153	43.4	35.0	0.005	1.36	0.98-1.89	0.066
	> 1,400	156	30.4	23.5				
Surgical margin	negative	272	41.7	33.9	<0.001	1.81	1.18- 2.78	0.006
	positive	47	12.4	7.4				
Macroscopic tumor type	IG	22	90.7	79.3	<0.001	3.29	0.98- 10.98	0.053
	MF	191	38.6	30.1				
	PI, PI+MF	129	24.1	19.4				
Biliary tract reconstruction	no	146	32.8	26.1	0.090			
	yes	195	41.3	33.3				
Extended lymph nodes dissection *	no	111	39.6	32.9	0.254			
	yes	228	42.7	34.1				
Histological differentiation	well	62	47.4	39.8	0.016	1.05	0.59- 1.90	0.864
	moderate	210	35.8	29.1				
	poorly	56	30.6	22.4				
Adjuvant chemotherapy following operation	no	270	37.1	28.7	0.451			
	yes	68	33.8	32.1				

* Lymph node dissection beyond the hepatoduodenal ligament nodes, including lymph nodes along the common hepatic artery and retropancreas and/or more distal lymph nodes

** Log-rank test

*** Cox regression analysis

and 25.1%, respectively. Among the patients with different macroscopic types of tumor, 15/22 patients (68.2%) with IG tumors survived more than 5 years and the rates of lymph node metastases were 0% in the IG tumors. The results of the univariable and multivariable analyses are summarized in Table 5. A univariate analysis demonstrated that significant prognostic factors for poorer survival were the preoperative high serum CA19-9 level ($>135\text{U/ml}$) ($p<0.001$), the presence of intrahepatic metastasis ($p<0.001$), a tumor size greater than 5 cm ($p<0.001$), massive bleeding of more than 1,400ml during surgery ($p=0.005$), the presence of positive surgical margins ($p<0.001$), macroscopic tumor type ($p<0.001$), the histological lymph node metastasis ($p<0.001$) and the histological differentiation ($p=0.016$). Gender, the presence of liver cirrhosis, the need for biliary tract reconstruction, extended lymph nodes dissection beyond the hepatoduodenal ligament, and the use of adjuvant chemotherapy after the surgery did not significantly correlate with patient survival following liver resection. We selected the following parameters for the multivariate analysis; tumor size, the number of tumors, the serum CA19-9 level, pathological lymph node metastasis, blood loss, surgical margin, histological differentiation, and macroscopic tumor type, because these parameters had p values less than 0.05 in univariate analysis. By using multivariable Cox proportional hazards regression analysis, significant factors affecting overall survival were the preoperative high serum CA19-9 level ($>135\text{U/ml}$) (hazard ratio: 2.07, $p<0.001$), the presence of intrahepatic metastasis (hazard ratio: 2.00, $p<0.001$), pathological lymph node metastasis (hazard ratio: 2.10, $p<0.001$), and a positive surgical margin (hazard ratio: 1.81, $p=0.006$). Among the patients who underwent extended lymphadenectomy beyond hepatoduodenal ligament nodes negative lymph node metastasis patients group showed statistically significant better survival than nodal involvement patients group in Fig. 1 (Log-rank test, $p<0.001$). The median survival of the 121 patients with nodal involvement was 12.2 months.

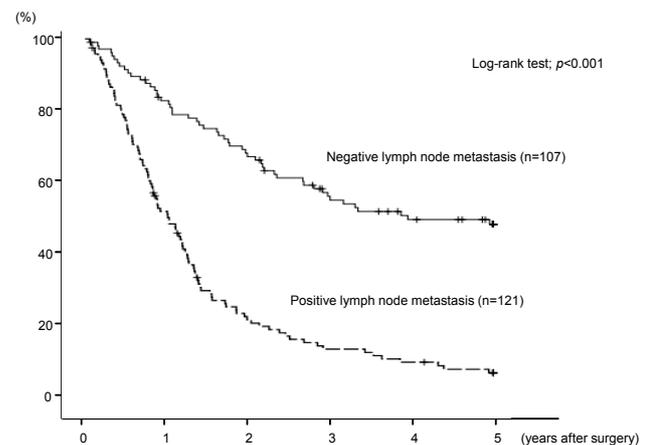


Fig. 1. Overall survival for the patients following extended lymphadenectomy beyond hepatoduodenal ligament

The predictor of the risk factors for lymph nodes metastases

The results of univariate and multivariate analyses are summarized in Table 6. Univariate analysis demonstrated that the significant risk factors for nodal involvement were the preoperative high serum CA19-9 level ($>135\text{U/ml}$) ($p<0.001$), macroscopic tumor type ($p<0.001$), presence of intrahepatic metastasis ($p=0.017$), and the histological differentiation ($p=0.006$). Using a multivariate logistic regression analysis, the significant factors predicting lymph node metastasis were the only preoperative high serum CA19-9 level ($>135\text{U/ml}$) (odds ratio: 5.34, $p<0.001$).

Table 6. Univariate and multivariate analysis of the predictor of the risk factors for lymph nodes metastases

Variables	number	Univariate analysis		Multivariate analysis		
		Lymph node metastasis negative / positive	p Value **	Odds ratio	95% C.I.	p Value ***
Tumor size	≤ 5cm	132	64/68	0.358		
	> 5cm	90	38/52			
The number of tumor	single	172	88/84	0.017	1	
	multiple	55	18/37		1.83	0.88-3.82 0.109
Serum CA19-9 (U/ml)	≤ 135	98	67/31	<0.001	1	
	> 135	123	36/87		5.34	2.77-10.27 <0.001
Macroscopic tumor type	IG	13	13/0	<0.001	—*	
	MF	104	49/55		1	
	PI, PI+MF	112	45/67		0.98	0.51-1.89 0.946
Histological differentiation	well	37	26/11	0.006	1	
	moderate	148	60/88		2.51	0.98-6.47 0.056
	poorly	30	11/19		2.32	0.70-7.69 0.171

Patients with extended lymphadenectomy : n=228

* Not detected because of no lymph node metastasis

** Chi-square analysis

*** Logistic regression analysis

Conclusion

These present data was retrospectively collected by the various institutes with different strategy for node dissection for ICC patients, but these results suggest that the extended lymphnode dissection may not be required to prolong the survival time. Therefore, further prospective studies, including randomized controlled trials, may be needed to clarify the impact of lymph node dissection, including extended lymphadenectomy, on ICC patients.