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Surgical Outcome and Prognostic Factors in Intrahepatic Cholangiocarcinoma

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Abstract
Background The clinicopathologic features and surgical outcome of intrahepatic cholangiocarcinoma are not fully understood.
Methods Fifty-six consecutive patients with intrahepatic cholangiocarcinoma who underwent surgical resection at the National Cancer Center Hospital East between October 1992 and July 2007 were retrospectively analyzed. Intrahepatic cholangiocarcinomas were subdivided into solitary tumors and tumors with intrahepatic metastasis.
Results Complete tumor removal (R0 resection) was performed in 42 patients (75%). The 5-year survival rate for patients with intrahepatic cholangiocarcinoma ($n = 56$), patients with a solitary tumor ($n = 46$), and patients with intrahepatic metastasis ($n = 10$) were 32, 38, and 0%, respectively. There was a significant difference in survival between patients with a solitary tumor and those with intrahepatic metastasis ($p < 0.0001$). The 5-year survival rate for patients with stage I ($n = 3$), II ($n = 9$), III ($n = 15$), and IV disease ($n = 26$) was 100, 67, 37, and 0%, respectively. There was a significant difference in survival between stage I and stage IV ($p = 0.011$), between stage II and stage IV ($p = 0.0002$), and between stage III and stage IV ($p = 0.0015$). The most frequent site of recurrence was the liver. Univariate analysis showed that intrahepatic metastasis, portal vein invasion, hepatic duct invasion, lymph node metastasis, perineural invasion, and positive surgical margin (R1) were significantly associated with poor survival. Multivariate analysis confirmed that intrahepatic metastasis was a significant and independent prognostic indicator after surgical resection for intrahepatic cholangiocarcinoma ($p = 0.001$). No patient with intrahepatic metastasis survived more than 10 months in this study.
Conclusions Intrahepatic metastasis was the strongest predictor of poor survival in intrahepatic cholangiocarcinoma.

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Introduction

Intrahepatic cholangiocarcinoma is an uncommon hepatic neoplasm compared with hepatocellular carcinoma. Intrahepatic cholangiocarcinoma comprises 4.1% of primary liver cancer in Japan [1]. Recent reports suggest that the incidence of intrahepatic cholangiocarcinoma has significantly increased in Scotland [2], England and Wales [3], and the United States [4, 5]. However, the clinocopathologic features and surgical outcome of this neoplasm are not fully understood because of the limited number of cases. Intrahepatic cholangiocarcinoma is generally considered to be a highly malignant adenocarcinoma, because this neoplasm is frequently associated with nodal involvement, intrahepatic metastasis, peritoneal dissemination, or invasion into the bile duct and portal vein in the hepatic hilus [6–12]. Effective chemotherapeutic regimens have not been established for intrahepatic cholangiocarcinoma [13–15]. Although surgical resection offers the only chance of cure in patients with intrahepatic cholangiocarcinoma, the 5-year survival rate is 20–40% for patients with potentially curative resection [6, 8–10, 16]. Prognostic factors that influence survival after surgical resection have not been well defined. Thus, it is difficult to correctly predict survival after surgical treatment. The present single-institution study examined

the clinicopathologic features of intrahepatic cholangiocarcinoma and evaluated prognostic factors predicting survival after surgical resection.

Patients and methods

Fifty-six consecutive patients with intrahepatic cholangiocarcinoma who underwent surgical resection at the National Cancer Center Hospital East between October 1992 and July 2007 were retrospectively analyzed. All 56 patients were followed up after operation. Patient follow-up ranged from 1 to 104 (median, 14) months. Overall survival analysis included all deaths, such as in-hospital death or death due to an unrelated cause. Tumors were staged according to the classification of primary liver tumors proposed by the Liver Cancer Study Group of Japan [17]. Hilar cholangiocarcinoma (Bismuth type I, II, III, or IV) and combined hepatocellular and cholangicarcinoma were excluded from this study.

Preoperative imaging workup was performed to evaluate the extent of the disease. This included computed tomography (CT), magnetic resonance imaging (MRI), and abdominal ultrasonography. In addition, in selected patients percutaneous transhepatic cholangiography, endoscopic retrograde cholangiography, or magnetic resonance cholangiopancreatography (MRCP) was performed. To relieve obstructive jaundice, percutaneous transhepatic biliary drainage (PTBD) was performed in 11 patients, endoscopic retrograde biliary drainage in 1 patient, and endoscopic nasogastric biliary drainage in 1 patient, respectively. No patient underwent staging laparoscopy in this series.

Clinicopathologic factors likely to influence survival after surgical resection were analyzed by Kaplan-Meier survival analysis and multivariate analysis. Statistical analysis was performed by χ^2 test and Student's *t*-test, when appropriate. Cumulative survival rates were generated by Kaplan-Meier method. The survival curves were compared by log-rank test. Significant factors identified by univariate analysis were further examined by multivariate analysis. Multivariate regression analysis was performed with the Cox hazards model using SPSS software: Dr. SPSS 2 for Windows (SPSS Japan Inc., Tokyo). Differences were considered significant at $p < 0.05$.

Results

The characteristics of the patients with intrahepatic cholangiocarcinoma are shown in Table 1. Intrahepatic cholangiocarcinoma was classified into mass-forming type ($n = 41$), periductal infiltrating type ($n = 12$), or intraductal growth type ($n = 3$) according to the classification of primary liver tumors proposed by the Liver Cancer Study Group of Japan [17]. Intrahepatic cholangiocarcinomas were subdivided into solitary tumors ($n = 46$) and tumors with intrahepatic metastasis ($n = 10$). There were 39 men and 17 women, with a mean age of 66 years. Fifteen patients (27%) had jaundice, 9 (16%) had abdominal pain, and 3 (5%) had loss of appetite, whereas 30 (54%) had no symptoms. Regarding the maximum tumor size, the mean size of all intrahepatic cholangiocarcinomas ($n = 56$), solitary tumors ($n = 46$), and tumors with intrahepatic metastasis ($n = 10$) was 5.2 (range, 1.4–12.5), 4.7 (range, 1.4–11), and 7.3 cm (range, 3.7–12.5), respectively. There was a significant difference in maximum tumor size between solitary tumors and tumors with intrahepatic metastasis ($p = 0.018$). There was no tendency for intrahepatic cholangiocarcinoma to be located in the left or right lobe. The histologic findings are tabulated in Table 2. Thirty-one intrahepatic cholangiocarcinomas had perineural invasion, 24 had invasion of the left or right hepatic duct, 21 had lymph node metastasis, and 38 had portal vein invasion. All patients with intrahepatic metastasis had portal vein invasion.

Complete tumor removal (R0 resection) was performed in 42 patients (75%). Seventy-eight percent (36/46) of patients with a solitary tumor had margin-negative R0 resection, whereas 60% (6/10) of patients with intrahepatic metastasis had R0 resection. The hepatic margin was involved in five patients (3 solitary tumors, 2 tumors with intrahepatic metastasis); the bile duct margin was involved

Table 1 Characteristics of intrahepatic cholangiocarcinoma

Patients' characteristics	Total ($n = 56$)	Solitary ($n = 46$)	IM ($n = 10$)
Mean age (year)	66	66	67
Sex (male/female)	39/17	31/15	8/2
Symptoms			
Jaundice	15	13	2
Abdominal pain	9	6	3
Loss of appetite	3	3	0
No symptom	30	26	4
Mean size (cm)	5.2	4.7	7.3
Macroscopic type			
Mass-forming type	41	32	9
Periductal infiltrating type	12	11	1
Intraductal growth type	3	3	0
Location (right/left)	31/25	24/22	7/3
Elevated serum CEA	23	22	1
Elevated serum CA19-9	33	24	9

IM intrahepatic cholangiocarcinoma with intrahepatic metastasis, *CEA* carcinoembryonic antigen

Table 2 Histologic findings of intrahepatic cholangiocarcinoma

Histologic findings	Total ($n = 56$)	Solitary ($n = 46$)	IM ($n = 10$)
Perineural invasion	31	25	6
Invasion of the hepatic duct	24	20	4
Lymph node metastasis	21	16	5
Portal vein invasion	38	28	10
Histological differentiation			
Well differentiated	12	11	1
Moderately differentiated	30	26	4
Poorly differentiated	11	6	5
Others	3	3	0
Margin status			
R0	42	36	6
R1	14	10	4
Stage			
I	3	3	0
II	9	9	0
III	16	16	0
IV	25	15	10

IM intrahepatic cholangiocarcinoma with intrahepatic metastasis

in four patients (3 solitary tumors, 1 tumor with intrahepatic metastasis); and the dissected tissue margin was involved in nine patients (8 solitary tumors, 1 tumor with intrahepatic metastasis).

Patients with intrahepatic cholangiocarcinoma were treated by extended left hepatectomy ($n = 24$), extended right hepatectomy ($n = 17$), right trisegmentectomy ($n = 3$), segmentectomy ($n = 2$), or subsegmentectoy or partial hepatectomy ($n = 10$). In addition, the following procedures were performed: extrahepatic bile duct resection ($n = 24$), portal vein resection with end-to-end anastomosis ($n = 8$), hepatic artery resection with end-to-end anastomosis ($n = 2$), and partial resection of the inferior vena cave ($n = 3$). The operative procedures are summarized in Table 3.

The survival curves after surgical treatment are shown in Figs. 1–3. The overall 1-, 3-, and 5-year survival rates for patients with intrahepatic cholangiocarcinoma were 59, 42, and 32%, respectively, with a median survival of 22 months (Fig. 1). The 1-, 3-, and 5-year survival rates and a median survival for patients with a solitary tumor ($n = 46$) and those with intrahepatic metastasis ($n = 10$) were 70%, 49%, 38%, 35 months, and 0%, 0%, 0%, 5 months, respectively (Fig. 2). There was a significant difference in survival between patients with a solitary tumor and those with intrahepatic metastasis ($p < 0.0001$). The 5-year survival rate for patients with stage I ($n = 3$), II ($n = 9$), III ($n = 15$), and IV disease ($n = 26$) was 100, 67, 37 and 0%, respectively (Fig. 3). There was a

Table 3 Operative procedures for intrahepatic cholangiocarcinoma

Operative procedures	Total	Solitary	IM
Extended right hepatectomy	17	13	4
Right trisegmentectomy	3	2	1
Extended left hepatectomy	24	21	3
Segmentectomy	2	1	1
Subsegmentectomy or partial hepatectomy	10	9	1
Additional procedures			
Extrahepatic bile duct resection	24	20	4
Portal vein resection	8	6	2
Hepatic artery resection	2	1	1
Inferior vena cava resection	3	2	1

IM intrahepatic cholangiocarcinoma with intrahepatic metastasis

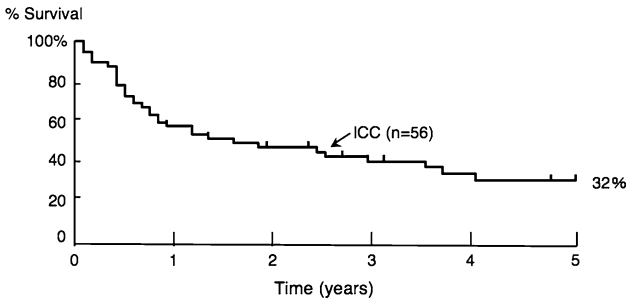

Fig. 1 Survival rate for patients with intrahepatic cholangiocarcinoma ($n = 56$) The overall 1-, 3-, and 5-year survival rates for patients with intrahepatic cholangiocarcinoma were 59, 42, and 32%, respectively

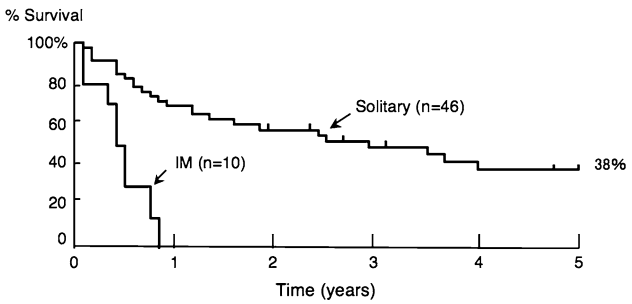

Fig. 2 Survival rates for patient with solitary intrahepatic cholangiocarcinoma ($n = 46$) and those with intrahepatic metastasis ($n = 10$). The 1-, 3-, and 5-year survival rates and a median survival for patients with a solitary tumor (n = 46) and those with intrahepatic metastasis ($n = 10$) were 70%, 49%, 38%, 35 months, and 0%, 0%, 0%, 5 months, respectively. There was a significant difference in survival between patients with solitary tumors and those with intrahepatic metastasis ($p < 0.0001$)

significant difference in survival between stage I and stage IV ($p = 0.011$), between stage II and stage IV ($p = 0.0002$), and between stage III and stage IV ($p = 0.0015$). The 5-year survival rate for patients with mass-forming type ($n = 41$), periductal infiltrating type

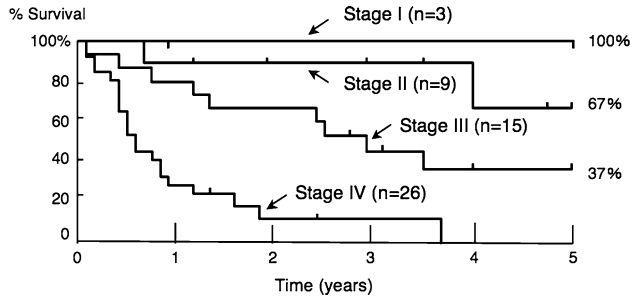

Fig. 3 Survival rates for patient with stage I ($n = 3$), II ($n = 9$), III ($n = 15$), and IV disease ($n = 26$). The 5-year survival rate for patients with stage I, II, III, and IV disease ($n = 29$) was 100, 67, 37, and 0%, respectively. There was a significant difference in survival between stage I and stage IV ($p = 0.011$), between stage II and stage IV ($p = 0.0002$), and between stage III and stage IV ($p = 0.0015$)

($n = 12$), and intraductal growth type ($n = 3$) was 34, 17, and 67%, respectively. There was no significant difference in survival between patients with mass-forming type and those with periductal infiltrating type ($p = 0.25$).

The number of cases of disease recurrence and death after surgical resection are shown in Table 4. Recurrent disease occurred in 26 patients with a solitary tumor and 5 patients with intrahepatic metastasis. Sites of recurrence were as follows: intrahepatic ($n = 18$), hepatic hilus (locoregional) ($n = 14$), peritoneum ($n = 7$), para-aortic lymph node ($n = 5$), bone ($n = 2$), thoracic lymph node ($n = 2$), lung ($n = 1$), neck lymph node ($n = 1$), stomach ($n = 1$), and skin ($n = 1$). The most frequent site of recurrence was the liver. Four disease-free patients died of unrelated causes, such as brain hemorrhage, pneumonia, and lung cancer. Two patients are alive with disease recurrence. Five patients had in-hospital death as a result of hepatic failure ($n = 3$), sepsis ($n = 1$), or rapid peritoneal dissemination ($n = 1$). Of the three patients who died of hepatic failure, each patient had a vascular complication, such as portal vein thrombus, hemorrhage from the hepatic artery, and infection of inferior vena cava graft. Five patients underwent a secondary resection for liver metastasis ($n = 3$) or lymph node metastasis ($n = 2$) a median of 18 (range, 18–67) months after the first operation. Three of these five patients are still alive without recurrent disease.

Table 4 Number of cases of disease recurrence and death after surgical resection

	Total	Solitary	IM
No. of deaths	36	27	9
In-hospital death	5	3	2
Death due to recurrence	26	21	5
Death from other causes in disease-free patients	5	3	2
No. of recurrences	31	26	5
Recurrent site			
Intrahepatic	18	13	5
Hepatic hilus (locoregional)	14	13	1
Peritoneum	7	6	1
Para-aortic lymph node	5	4	1
Bone	2	1	1
Thoracic lymph node	2	2	0
Lung	1	1	0
Neck lymph node	1	1	0
Stomach	1	1	0
Skin	1	1	0

IM intrahepatic cholangiocarcinoma with intrahepatic metastasis

The following 13 factors were analyzed by Kaplan-Meier survival analysis and multivariate analysis: age (<65 vs. ≥65 years), sex, macroscopic type (mass-forming type vs. periductal infiltrating type), invasion of the left or right hepatic duct, tumor size (<5 vs. ≥5 cm), histology (well-differentiated adenocarcinomas vs. others), portal vein invasion, perineural invasion, lymph node metastasis, intrahepatic metastasis, margin status (R0 vs. R1 resection), serum carcinoembryonic antigen (<5 vs. ≥5 ng/ml), and serum carbohydrate antigen19–9 (<37 vs. ≥37 U/ml). We used our hospital cutoff levels of carcinoembryonic antigen (5 ng/ml) and carbohydrate antigen19–9 (37 U/ml). The cutoff levels for age and tumor size were chosen as approximate values of median age (66 years) and median tumor size (4.8 cm). Clinicopathologic factors are shown in Table 5. Among 13 factors, 6 were significantly associated with outcome in univariate analysis: hepatic duct invasion ($p = 0.0009$), portal vein invasion ($p = 0.0004$), perineural invasion ($p = 0.0002$), lymph node metastasis ($p = 0.0006$), margin status ($p = 0.012$), and intrahepatic metastasis ($p < 0.0001$). Multivariate analysis using the Cox proportional hazards model was completed for six factors, with $p < 0.05$ in univariate analysis. Multivariate analysis confirmed that intrahepatic metastasis ($p = 0.001$) was a significant and independent prognostic indicator after surgical resection for intrahepatic cholangiocarcinoma (Table 6). No patient with intrahepatic metastasis survived more than 10 months.

Discussion

The clinicopathologic features and surgical outcome of intrahepatic cholangiocarcinoma have not been fully clarified because of the limited number of cases. Previous studies have shown that tumor-associated biological factors, such as lymph node status, tumor size, intrahepatic metastasis, and invasion of the portal vein, are important in the outcome of intrahepatic cholangiocarcinoma [6–12, 16]. Ohtsuka et al. [16] reported that multiple hepatic lesions and high serum CA19-9 concentration were significantly related to a poor outcome. Nakagawa et al. [18]

Table 5 Univariate analysis of potential predictors of overall survival after surgical resection

	No.	Survival (%)			*p* value
		1 year	3 years	5 years	
Age (year)					
<65	24	54	36	24	0.72
≥65	32	62	44	38	
Sex					
Male	39	56	41	33	0.88
Female	17	65	41	27	
Macroscopic type					
MS type	41	61	49	34	0.25
PI type	12	50	17	17	
Hepatic duct invasion					
Negative	32	68	61	50	0.0009
Positive	24	46	16	8	
Tumor size (cm)					
<5	29	69	53	47	0.25
≥5	27	47	31	22	
Histology					
Well	12	83	63	63	0.066
Others	44	52	35	21	
Portal vein invasion					
Negative	18	78	78	69	0.0004
Positive	38	49	23	12	
Perineural invasion					
Negative	25	72	67	60	0.0002
Positive	31	47	18	7	
Lymph node metastasis					
Negative	35	71	55	47	0.0006
Positive	21	36	16	0	
Intrahepatic metastasis					
Negative	46	70	49	38	<0.0001
Positive	10	0	0	0	
Margin status					
R0	42	69	51	39	0.012
R1	14	29	14	14	
Serum CEA (ng/ml)					
<5	34	64	45	28	0.99
≥5	22	50	36	36	
Serum CA19-9 (U/ml)					
<37	19	79	59	37	0.066
≥37	33	41	27	27	

MS type mass-forming type, *PI type* periductal infiltrating type

reported that multiple tumor and noncurative resection were significant risk factors for poor survival. This study showed that intrahepatic metastasis was an independent predictor of poor survival in patients with intrahepatic cholangiocarcinoma, and no patient with intrahepatic metastasis survived more than 10 months. These results

Table 6 Multivariate Cox regression analysis of prognostic factors after surgical resection

Factors	Relative risk (95% CI)	*p* value
Intrahepatic metastasis	5.38 (2.07–14)	0.001
Portal vein invasion	1.99 (0.56–7.06)	0.28
Hepatic duct invasion	1.87 (0.76–4.6)	0.17
Lymph node metastases	1.52 (0.65–3.57)	0.33
Perineural invasion	1.45 (0.45–4.72	0.53
Margin status (R1)	1.25 (0.59–2.64)	0.56

suggest that intrahepatic metastasis is strongly associated with poor survival. Thus, the efficacy of hepatic resection for intrahepatic cholangiocarcinoma with intrahepatic metastasis is controversial because of little survival benefit of aggressive surgical resection. Further confirmatory studies are needed to evaluate the role of hepatic resection for intrahepatic cholangiocarcinoma with intrahepatic metastasis.

Concerning the surgical treatment for intrahepatic cholangiocarcinoma, improved survival results after curative R0 resection have been reported in recent years [6–8, 19–21]. Lang et al. [19] reported that the calculated median survival and 1- and 3-year survival rates were 46 months, 94% and 82% after R0 resection for intrahepatic cholangiocarcinoma, and they concluded that R0 resection could provide prolonged survival, even in patients with advanced intrahepatic cholangiocarcinoma. Madariaga et al. [6] and Inoue et al. [20] reported that the surgical margin was an independently significant indicator for survival. In our series, margin-negative R0 resection was significantly associated with a favorable outcome in univariate analysis. The 5-year survival rates for patients with R0 resection and R1 resection were 38% and 14%, respectively. These studies suggested that better survival results could be achieved by margin-negative R0 resection, including vascular resection for intrahepatic cholangiocarcinoma.

However, the survival benefit of portal vein or hepatic artery resection for intrahepatic cholangiocarcinoma is controversial. Intrahepatic cholangiocarcinoma involving the portal vein or hepatic artery in the hepatic hilus seems to be a locally advanced disease and is classified as stage III or more according to the UICC staging system [22]. The survival of patients with intrahepatic cholangiocarcinoma involving the portal vein or hepatic artery has been seldom reported because of the limited number of cases [18, 19, 23–25]. Yamamoto et al. [23] reported 12 cases of portal vein resection for intrahepatic cholangiocarcinoma, Lang et al. [19] reported 5 cases, Miwa et al. reported [24] 4 cases, and Nakagawa et al. [18] reported 2 cases. In this study, eight patients underwent portal vein resection and reconstruction. Histopathologic study revealed that seven

of eight patients had definite portal vein invasion. The 1-, 3-, and 5-year survival rates for patients with portal vein resection were 38, 25, and 0%. There was no significant difference in survival between patients with and without portal vein invasion ($p = 0.21$). One patient was alive and disease-free more than 42 months after extended left hepatectomy with both portal vein and hepatic artery resection. Although resection offers the only chance of long-term survival, patients with intrahepatic cholangiocarcinoma involving the portal vein or hepatic artery in the hepatic hilus frequently develop recurrent disease after surgery. Despite its high morbidity, such aggressive vascular resection should be considered for selected intrahepatic cholangiocarcinoma patients whose disease seems to be potentially resectable with a negative-margin on preoperative imaging and intraoperative findings. Further studies are needed to evaluate the efficacy of extended hepatectomy with portal vein or hepatic artery resection for intrahepatic cholangiocarcinoma.

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