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Pattern and Outcome of Recurrence After Resection for Intrahepatic Cholangiocarcinoma: Retrospective Analysis for Experience and Outcomes from A Single Institution

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Keywords:

Intrahepatic cholangiocarcinoma; Recurrence; Recurrence free survival; Recurrence pattern; Treatment modality

Abbreviations:

ICC: Intrahepatic Cholangiocarcinoma**;** RFS: Recurrence-Free Survival**;** PRS: Post-Recurrence Survival; OS: Overall Survival; IH: Intrahepatic; EH: Extrahepatic**;** TACE: Transarterial Chemoembolization**;** RFA: Radiofrequency ablation**;** BMI: Body Mass Index; DM: Diabetes Mellitus CA 19-9 Carbohydrate Antigen 19-9; CEA: Carcinoembryonic Antigen; CT: Computed Tomography; RBC: Red Blood Cell

1. Abstract

1.1. Aims: This study aimed to analyze recurrence-free survival (RFS), post-recurrence survival (PRS) based on ICC recurrence patterns and treatment modalities.

1.2. Methods: Medical records of patients undergoing curative resection for ICC in a single institution were retrospectively reviewed. RFS, the first recurrence site, recurrence management, PRS, and factors associated with recurrence patterns and PRS were investigated.

1.3. Results: A total of 147 patients were enrolled. During a median follow-up of 36.1 months, 101 patients (68.7%) experienced ICC recurrence including marginal (n = 12, 11.9%), intrahepatic (IH, n = 28, 27.7%), extrahepatic (EH, n = 41, 40.6%), and both IH + EH recurrence (n = 20, 19.8%). Median RFS of EH (7 vs. 9 months [IH], p = 0.026) and both IH + EH recurrence (median 5 vs. 9 months [IH], p = 0.005) was shorter compared with that of IH recurrence. PRS was the longest in IH recurrence (29 months), which was significantly longer than EH recurrence (9 months, p = 0.033) or IH + EH recurrence (4 months, p < 0.001). Lymph node (LN) metastasis was associated with an increased risk of EH ± IH recurrence (HR 3.061, 95% confidence interval 1.115–8.403; p = 0.03). Patients who received local treatment had longer PRS than those with other treatments. LN metastasis, shorter RFS, and no surgical treatment showed unfavorable effect on PRS.

1.4. Conclusions. Patients with EH ± IH recurrence showed shorter RFS and worse PRS than other recurrence types. PRS was favorable in patients with longer RFS and locoregionally treatable recurrence.

2. Introduction

Intrahepatic cholangiocarcinoma (ICC) is a rare malignant tumor originating from epithelial cells lining second-order or more peripheral branches of the intrahepatic bile ducts [1,2]. t is the second most common liver malignancy after hepatocellular carcinoma (HCC), accounting for 10%–12% of all liver cancers [3,4]. ICC is associated with a poor prognosis because it usually presents at an advanced stage and progresses rapidly. Surgical resection remains the only curative treatment that offers the best chance of survival for ICC patients. However, ICC cure rates following surgical resection is low, with postoperative recurrence rates reported to be as high as 70 % [5-7]. Furthermore, the prognosis of patients with recurrent ICC after primary resection is dismal. Given the low incidence and resectability of ICC, there is a lack of information regarding the long-term outcomes of ICC, its recurrence pattern, and the prognostic effect of treatment on recurrent ICC. The majority of

previous studies on ICC recurrence have classified recurrence into intrahepatic (IH), extrahepatic (EH), and combined patterns [8,9]. In a recent study by Hu et al., IH recurrence was further classified as marginal and non-marginal recurrence, with the former showing the worst disease-free survival (DFS) and prognosis among the other recurrence patterns [10]. Additionally, narrow resection margins were reported as one of the independent risk factors for a poor prognosis following resection. However, it is hard to conclude that marginal recurrence is the most unfavorable recurrence pattern because there is no other study comparing these recurrence patterns. In our previous study of 81 patients with recurrent ICC, overall survival (OS) rates at 1, 3, and 5 years after recurrence were 47%, 23%, and 15%, respectively. Patients with IH recurrence exhibited a better prognosis than those with EH or combined IH + EH recurrence patterns. In our previous study, local treatment modalities such as surgery, transarterial chemoembolization (TACE), and radiofrequency ablation (RFA) were found to be effective for OS after recurrence in patients with localized IH and EH recurrences [11]. Nevertheless, the optimal treatment of recurrent ICC after resection has not been established yet. The National Comprehensive Cancer Network (NCCN) guidelines (2020) for hepatobiliary cancers do not contain treatment recommendations for recurrent ICC. Moreover, the European Association for the Study of the Liver guidelines (2014) guidelines on ICC management only state that resection or ablation may be attempted in cases of IH recurrence, without providing any additional information [12]. Although the general consensus is to avoid further therapy in cases of postoperative IH or EH recurrence after surgery, several modalities have recently been reported to achieve varying degrees of success, including secondary surgery, chemotherapy, radiotherapy, RFA, and TACE [10,13-15]. In this study, we aimed to analyze recurrence-free survival (RFS) and post-recurrence survival (PRS) in recurrent ICC patients based on ICC recurrence patterns and to investigate their response to various treatment modalities. We also tried to identify the factors associated with recurrence patterns and prognosis after recurrence.

3. Material and Methods

3.1. Study Population and Data Collection

The medical records of 147 patients undergoing curative-intent hepatectomy for ICC at the National Cancer Center, Korea between March 2001 and July 2017 were retrospectively reviewed. Pathologically confirmed ICC cases after surgery were included in the study. Patients with hilar cholangiocarcinoma, unresectable ICC, and combined hepatocellular cholangiocarcinoma were excluded from the final analysis. Pathological staging for all subjects was reassigned according to the 8th edition of the American Joint Committee on Cancer staging guidelines [16]. Positive margins were defined as macroscopic or microscopic tumor involvement of resection margins. R0 resection was defined as a margin clearance of >0 mm. Recurrence was determined by 1 or more imaging modalities, such as abdominal computed tomography (CT), magnetic resonance imaging, and positron emission tomography-CT, or biopsy. Patient characteristics included age, gender, body mass index, diabetes mellitus, hypertension, smoking history, drinking history [17], liver cirrhosis, hepatitis B virus (HBV) serological status, preoperative serum carcinoembryonic antigen level, and preoperative serum carbohydrate antigen (CA 19-9) level. Radiological and pathological factors were as follows: tumor vascularity on CT, tumor size, tumor multiplicity, macrovascular invasion, microvascular invasion, perineural invasion, bile duct invasion, tumor stage, cell differentiation status, margin status, lymph node (LN) metastasis, and whether major hepatectomy (i.e., resection of ≥3 segments) was performed. Surgical outcomes included estimated blood loss, operative time, major complications (Clavien-Dindo classification, grade 3 or 4) [18], adjuvant treatment (at least 1 cycle of chemotherapy or a complete course of radiation therapy), and perioperative (within 1 week preoperatively and 4 weeks postoperatively) red blood cell (RBC) transfusion. This study was approved by the Institutional Review Board of National Cancer Center, Korea) (NCC2020-0131).

3.2. Surgery and Perioperative Management Protocols

Standardized surgical techniques and postoperative management protocols were used for all ICC patients during the study period. During hepatectomy for ICC, LN #station 12 was dissected if the tumor resided in the right hepatic lobe, depending on the surgeons' preferences. If the tumor was located at the left hepatic lobe, LN #stations 3 and #12 were dissected. However, when enlargement of other LNs was detected preoperatively (on radiological images) or intraoperatively, additional LN dissection was performed at the surgeon's discretion. RBC transfusion was required in patients with significant perioperative blood loss, serum hemoglobin levels of <7 g/dL, or hemoglobin levels of 7–10 g/dL combined with any symptoms or signs of acute bleeding. Except for the patients with early stage ICC (T1 or T2) without LN metastasis and a clear resection margin, those who refused to receive the adjuvant treatment, and those with an intolerable general condition, patients who recovered after surgery received adjuvant treatment at 6─8 weeks after surgery. Chemotherapy regimens were either 5-fluorouracil (5-FU) based (5–15 mg/kg) or gemcitabine-based (1 g/m^2). Adjuvant concurrent chemoradiation therapy was applied at a dose of 5040 cGy in 28 fractions, with 5-FU or gemcitabine given on the first and last 3 days.

3.3. Follow-Up Assessment and Classification of Recurrence Patterns of ICC

Follow-up examinations included tumor marker measurement, other laboratory tests, chest CT, and abdominopelvic CT. Follow-up data until December 2019 were obtained from the medical records. Patients were followed up monthly during the first 3 months, quarterly during the first 2 years, and biannually thereafter. Recurrence was determined by radiological analysis or biopsy. ICC recurrence patterns were grouped as being IH, marginal, EH, and both IH and EH. Marginal recurrence was defined as recurrence in the surgical bed or within the same segment as the primary tumor; IH recurrence, recur-

rent disease in the liver outside of the previously treated segment; EH recurrence, tumor recurrence anywhere outside of the liver; and both IH+EH, simultaneous IH and EH recurrence.

3.4. Principles of Treatment for Recurrent ICC

The basic principles of treatment for recurrent ICC in our institution were as follows: (1) surgical resection for either IH or EH recurrence (if the lesion was localized and respectable), which was attempted if the patient's general condition was suitable for surgery; (2) local treatments including TACE (if the tumor showed partial enhancement on radiological examination) or RFA (if recurrences were small in size and fewer than 3 in number) for IH recurrence, which were used when surgery was contraindicated-e.g., due to impaired liver function (Child-Pugh class B/C); (3) systemic therapy including chemotherapy and radiotherapy for advanced or inoperable recurrences; and (4) supportive care, which was provided to inoperable patients or those refusing to receive any of the above treatments.

3.5. Statistical Analysis

Differences between groups of categorical variables were compared using Fisher's exact test or Pearson's chi-squared test. Continuous variables were compared and analyzed using the two-sample t-test and Wilcoxon rank-sum test. The Kaplan-Meier method was used to estimate survival curves; the log-rank test, to compare significant differences between survival curves; and the Cox proportional hazards model, to identify prognostic factors for recurrence (with recurrence considered as an event). In the multivariate model, factors with $p < 0.1$ were retained through backward elimination after significant factors were included in the univariate model. Data were analyzed using SAS 9.4 version (SAS Institute Inc., Cary, NC, USA) and the R Foundation for Statistical Computing (version 3.6.2). A two tailed $p < 0.05$ was considered statistically significant.

4. Results

4.1. Patient Characteristics

A total of 147 patients were included, of whom 101 (68.7%) experienced ICC recurrence (recurrence group). The median follow-up duration after hepatectomy was 36.1 months, and the median RFS was 12.0 months (Figure 1a). The log-rank test showed OS rates were significantly lower in the recurrence group (1-, 3-, 5-year survival rates were 68.3%, 38.0%, and 25.2%, respectively) compared with the non-recurrence group (1-, 3-, 5-year survival rates were 87.0%, 75.4%, and 75.4%, respectively; $p<0.001$) (Figure 1b). In the recurrence group, the proportion of patients with current smoking, HBV, high CA 19-9 levels (units/mL), hypovascular ICC, large tumor (>5cm), microvascular invasion, perineural invasion, advanced T stage, and LN metastasis was higher than that in the non-recurrence group. On the other hand, the proportion of patients who received adjuvant treatment after primary surgery was lower in the non-recurrence group than in the recurrence group (Table 1).

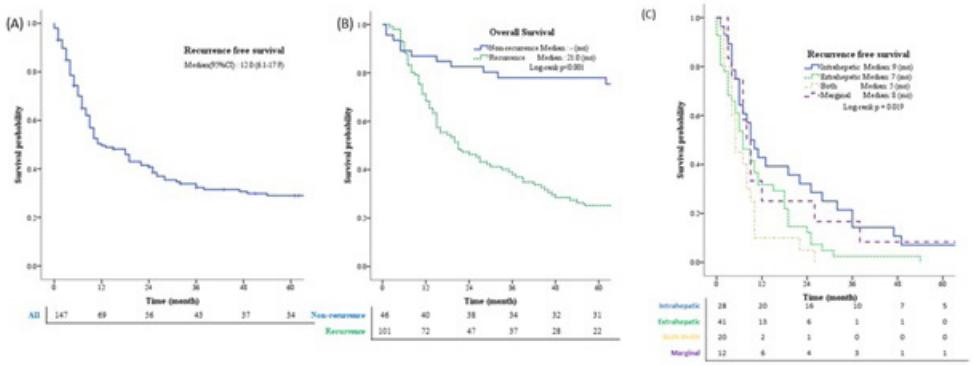

Figure 1: Kaplan-Meier curves of recurrence free survival and overall survival of patients with intrahepatic cholangiocarcinoma after surgery. (A) recurrence free survival of patients with intrahepatic cholangiocarcinoma, (B) overall survival according to whether recurrence, (C) recurrence free survival according to recurrence patterns

Table 1: Baseline clinical and pathological characteristics

		Total	no recurrence	recurrence	p value	
Variable		(n = 147)	(n = 46)	(n = 101)		
Age, years						
	mean±sd	62.43±9.21	62.67±9.51	62.32±9.12	0.828	t
Gender						
	Male	103(70.07)	33(71.74)	70(69.31)	0.765	c
	Female	44(29.93)	13(28.26)	31(30.69)		
BMI (kg/m2)						
	mean±sd	23.69±3.19	23.94±2.93	23.58±3.31	0.524	t

DM						
		22 (14.97)	8 (17.39)	14 (13.86)	0.261	f
Hypertension						
		58 (39.46)	22 (47.83)	36 (35.64)	0.203	f
Smoking history						
	None	63 (42.86)	21 (46.65)	42 (41.58)	0.035	c
	Ex-smoker	39 (26.53)	17 (36.96)	22 (21.78)		
	Current	45 (30.61)	8 (17.39)	37 (36.64)		
Alcohol history						
	None	62 (42.18)	17 (36.96)	45 (44.55)	0.686	c
	Moderate	23 (15.65)	8 (17.39)	15 (14.85)		
	Heavy	62 (42.17)	21 (45.65)	41 (40.60)		
Liver cirrhosis		Missing=1	Missing=1			
		24(16.44)	10(22.22)	14(13.86)	0.208	c
Hepatitis B Virus						
		29(19.73)	14(30.43)	15(14.85)	0.028	c
CA19-9 (units/ml)		Missing = 17	Missing = 3	Missing = 14		
	median(Q1-Q3)	46.55(11-208)	26(8-82.5)	74(15.3-434)	0.021	w
	≤37	59(45.38)	25(58.14)	34(39.08)	0.04	c
	>37	71(54.62)	18(41.86)	53(60.92)		
CEA (ng/ml)		Missing = 29	Missing = 9	Missing = 20		
	median(Q1-Q3)	3.35(2.1-6.4)	2.9(2-5.7)	3.7(2.2-6.7)	0.199	w
	≤5	77(65.25)	26(70.27)	51(62.96)	0.439	c
	>5	41(34.75)	11(29.73)	30(37.04)		
Vascularity of mass on CT		Missing = 8	Missing = 5	Missing = 3		
	Hypervascular	23(16.55)	15(36.59)	8(8.16)	<.001	c
	Rim-enhanced	56(40.29)	17(41.46)	39(39.8)		
	Hypovascular	60(43.17)	9(21.95)	51(52.04)		
Tumor size (Cm)						
	mean±sd	5.41±2.58	4.44±2.37	5.86±2.56	0.002	t
	≤5	76(51.7)	32(69.57)	44(43.56)	0.003	c
	>5	71(48.3)	14(30.43)	57(56.44)		
Multiple lesions, ≥ 2						
		12(8.16)	3(6.52)	9(8.91)	0.754	f
Macrovascular invasion						
		26(17.69)	5(10.87)	21(20.79)	0.144	c
Microvascular invasion		Missing = 3		Missing = 3		
		65(45.14)	12(26.09)	53(54.08)	0.002	c
Perineural invasion		Missing = 17	Missing = 5	Missing = 12		
		51(39.23)	9(21.95)	42(47.19)	0.006	c
Biliary invasion		Missing = 16	Missing = 6	Missing = 10		
		64(48.85)	20(50)	44(48.35)	0.862	c
AJCC T category						
	T1–T2	94(63.95)	36(78.26)	58(57.43)	0.015	c
	T3–T4	53(36.05)	10(21.74)	43(42.57)		

Histological grade		Missing = 13	Missing = 3	Missing = 10		
	WD/MD	53(39.55)	19(44.19)	34(37.36)	0.451	c
	PD	81(60.45)	24(55.81)	57(62.64)		
Margin						
	Negative	126(85.71)	40(86.96)	86(85.15)	0.772	c
	Positive	21(14.29)	6(13.04)	15(14.85)		
Lymph node metastasis						
	No	84(57.14)	35(76.09)	49(48.51)	<.001	F
	Yes	34(23.13)	1(2.17)	33(32.67)		
	Unknown	29(19.73)	10(21.74)	19(18.81)		
Major hepatectomy						
		105(71.43)	32(69.57)	73(72.28)	0.736	c
Morphologic type		Missing = 5	Missing = 1	Missing = 4	0.212	F
	MF or IG	121 (85.21)	41 (91.11)	80 (82.47)		
	PI	21 (14.79)	4 (8.89)	17 (17.53)		
EBL (ml)						
	median(Q1-Q3)	500(300-800)	500(300-700)	500(350-800)	0.389	w
Operation time (min)						
	mean±sd	304.67±131.42	288.63±139.81	311.98±127.47	0.320	t
Major complications		Missing = 1		Missing = 1		
		23(15.75)	9(19.57)	14(14)	0.391	c
Adjuvant treatment						
		44(29.93)	5(10.87)	39(38.61)	0.001	c
Perioperative RBC transfusion						
		19(12.93)	5(10.87)	14(13.86)	0.616	c
BMI, body mass index; *DM*, Diabetes Mellitus; *CA 19-9*, Carbohydrate Antigen 19-9; *CEA*, carcinoembryonic antigen; *CT*, computed tomography; *WD*, well differentiated; *MD*, moderate differentiated; *PD*, poor differentiated; *MF*, mass forming; *IG*, intraductal growth; *PI*, periductal infiltrating; *EBL*, estimated blood loss; *RBC*, red blood cell						
t: Two sample t-test w: Wilcoxon rank sum test, c: Chi-square test, f: Fisher's exact test						

4.2. Types of Recurrence and RFS

In the cohort, 12 patients (11.9%) had recurrence at the marginal area, 28 (27.7%) had it within the liver away from the surgical margin (IH), 41 (40.6%) demonstrated recurrence at extrahepatic sites (EH), and 20 (19.8%) developed both IH + EH recurrence. Nearly 70% (69.3%) of all recurrences occurred within a year after primary surgical resection. EH recurrence (median 7 months) and both IH + EH recurrence (median 5 months) tended to occur earlier compared with IH recurrence (median 9 months; $p = 0.026$, and $p = 0.005$, respectively) (Figure 1c). However, there was no significant difference in RFS between IH recurrence group and marginal recurrence group (median 8 months; $p = 0.993$). In addition, RFS in the marginal recurrence group did not show significant difference compared with that in the EH recurrence ($p = 0.249$) and both IH + EH recurrence groups ($p = 0.100$).

4.3. Types of Recurrence and PRS

Among 101 patients with recurrent ICC, median OS after recurrence was 11 months (Figure 2a). Median PRS was longest in IH recurrence (29 months), which was significantly longer than that in EH recurrence (9 months, $p = 0.033$) or IH + EH recurrence (4 months, $p < 0.001$). There was no significant difference in PRS between IH and marginal recurrence (median 29 vs. 21 months, $p = 0.261$) groups. Patients with simultaneous IH + EH recurrence showed significantly shorter median PRS than that in patients with EH recurrence, and marginal recurrence ($p = 0.003$, and $p = 0.008$, respectively) (Figure 2b).

To identify the factors associated with EH and both IH+EH that showed unfavorable RFS and PRS ($n = 61$), we performed subgroup analysis. In univariate analysis, age, gender, history of diabetes mellitus, hypertension, smoking, alcohol, liver cirrhosis, HBV infection, preoperative serum CEA level, size and number of primary tumor, hepatic artery or microvascular invasion, histological grade, morphologic type, resection margin status of primary tumor, lymphadenectomy, adjuvant treatment, perioperative RBC transfusion, and major postoperative complications were not associated with EH with or without IH recurrence. In multivariate analysis, only LN metastasis with a hazard ratio of 3.061 and a 95% confidence interval (CI) of

1.115–8.403 (p = 0.03) displayed a significant association with EH with or without IH recurrence (Table 2). Patients with LN metastasis at primary hepatectomy showed shorter RFS for EH ± IH recurrence than those without LN metastasis at primary hepatectomy (10 vs. 5 months, p = 0.016, (Figure S1)

Contrary to EH±IH recurrence, IH recurrence was associated with body weight loss after initial diagnosis (HR 3.269, 95% CI 1.136-9.409, p = 0.028) and multiple primary ICC (HR 4.830, 95 CI 1.237-18.853, p = 0.023). Additionally, LN metastasis at primary hepatectomy was not associated with RFS in IH recurrence (p = 0.319)

4.4. Treatment Modalities for Recurrent ICC and PRS

The median PRS was better among patients undergoing any treatment modality for recurrent ICC than those receiving no treatment (17 vs. 5 months; p < 0.001, (Figure 2c). With respect to treatment modalities, local treatment including surgery (n = 14, 36 months) and TACE/RFA (n = 11, 38 months) led to a longer median PRS than did chemotherapy (n = 25, 15 months), radiation therapy or concurrent chemoradiotherapy (n = 13, 11 months). Additionally, significant differences in median PRS were observed between these treatment types (local vs. chemotherapy or CCRT, median 38 vs. 14 months, p = 0.039) (Figure 2d).

The proportion of treated patients was highest in the IH recurrence group (23/28, 82.1%), followed by the EH recurrence (27/40, 68.3%), marginal recurrence (7/12, 58.3%), and IH + EH (7/14, 33.3%) groups, respectively. The rate of local treatment (surgery or TACE/RFA) was 46.5% (13/28) in the IH recurrence group, 16.7% (2/12) in the marginal recurrence group, and 17.1% (7/41) in the EH recurrence group. In IH + EH recurrence group, 2 patients underwent surgical resection for recurrence, and 1 patient with multiple recurrence in the liver, lung, and adrenal gland received palliative RFA with RT for IH recurrence. Patients who survived longer than 36 months had more frequent IH recurrence, single site recurrence, or local treatment (surgery or TACE/RFA) group (Table S1).

In the analysis to identify the factors of PRS, LN metastasis (HR 4.576, 95% CI 1.317–15.893, p = 0.017), RFS shorter than one year (HR 8.449, 95% CI 1.788–39.921, p = 0.007), and surgical treatment for recurrence (HR 0.005, 95% CI 0–0.118, p = 0.001) were associated with PRS, independently (Table 3).

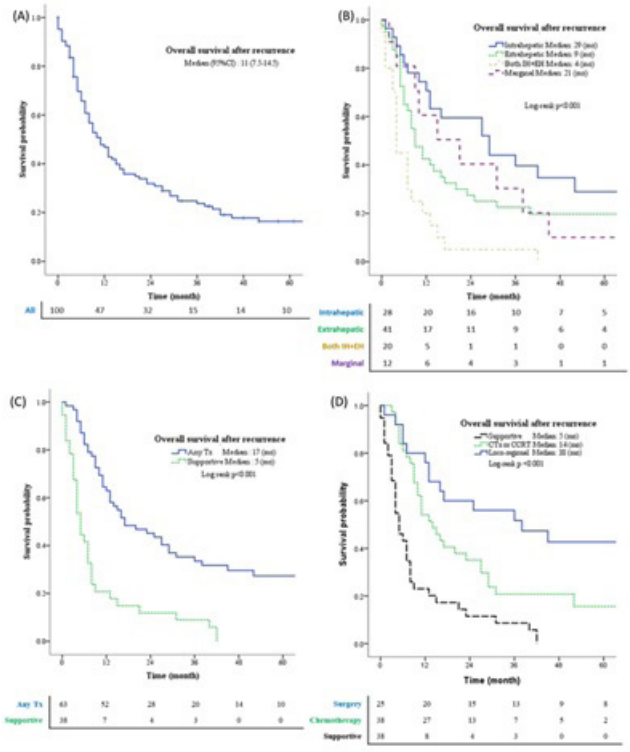

Figure 2: Kaplan-Meier curves of (A) post-recurrence survival, (B) post-recurrence survival according to recurrence pattern, (C) post-recurrence survival according to whether treatment, (D) post-recurrence survival according to type of treatment

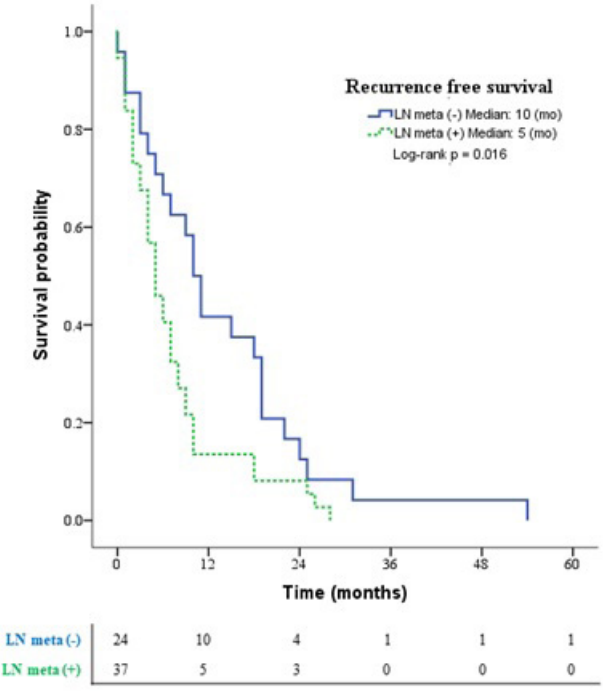

Figure S1: Recurrence free survival for extrahepatic±intrahepatic recurrence according to whether lymph node metastasis at primary hepatectomy for intrahepatic cholangiocarcinoma.

Table 2: Risk factor of extrahepatic with or without intrahepatic recurrence after primary operation for ICC (N=61)

Factors	No. of patients (%)	HR [95%CI]	P- value	HR [95%CI]	P- value
Bwt loss after initial diagnosis			0.021		0.455
-	28 (45.9)	1(ref)		1(ref)	
+	33 (54.1)	1.814 [1.095-3.107]		1.410 [0.572-3.473	
CA19-9 (units/ml)			0.015		0.176
≤37	20 (32.8)	1(ref)		1(ref)	
>37	34 (55.7)	2.100 [1.157-3.810]		1.734 [0.781-3.846]	
Vascularity of mass on CT			0.033		0.971
Hypervascular	5 (8.2)	1(ref)		1(ref)	
Rim-enhanced	23 (37.7)	1.587 [0.595-4.235]		1.098 [0.293-4.114]	
Hypovascular	32 (52.5)	2.828 [1.082-7.394]		0.988 [0.236-4.130]	
Portal vein invasion			0.077		0.393
No	50 (82.0)	1(ref)		1(ref)	
Yes	7 (11.5)	2.094 [0.924-4.748]		0.589 [0.174-1.987]	
Perineural invasion			0.037		0.689
No	25 (41.0)	1(ref)		1(ref)	
Yes	30 (49.2)	1.828 [1.038-3.220]		1.207 [0.480-3.039]	
Biliary invasion			0.096		0.871
No	25 (41.0)	1(ref)		1(ref)	
Yes	30 (49.2)	1.593 [0.921-2.755]		1.083 [0.415-2.830]	
AJCC T category			0.014		0.303
T1–T2	33 (54.1)	1(ref)		1(ref)	
T3–T4	28 (45.9)	1.931 [1.141-3.268]		1.589 [0.658-3.838]	

Lymph node metastasis			0.038		0.03
No	24 (39.3)	1(ref)		1(ref)	
Yes	23 (37.7)	2.197 [1.201-4.022]		3.061 [1.115-8.403]	
Unknown	14 (23.0)	1.510 [0.765-2.978]		1.554 [0.562-4.294]	
Bwt, body weight; *CA 19-9*, Carbohydrate Antigen 19-9; *CT*, computed tomography					

Table 3: Factors associated with post-recurrence overall survival of ICC.

Factors	No. of patients (%)	HR [95%CI]	P- value	HR [95%CI]	P- value
Bwt loss after initial diagnosis			0.023		0.071
-	47 (46.5%)	1(ref)		1(ref)	
+	54 (53.5%)	1.669 [1.074-2.595]		2.990 [0.909-9.830]	
CA19-9 (units/ml)			0.005		0.316
≤37	34 (39.1%)	1(ref)		1(ref)	
>37	53 (60.9%)	2.016 [1.238-3.284]		1.851 [0.555-6.174]	
Vascularity of mass on CT			0.048		0.722
Hypervascular	7 (7.2%)	1(ref)		1(ref)	
Rim-enhanced	40 (40.8%)	1.012 [0.419-2.447]	0.979	1.731 [0.074-40.494]	0.733
Hypovascular	51 (52.0%)	1.777 [0.755-4.179]	0.188	1.009 [0.029-35.712]	0.996
Vascularity of recur mass on CT			0.001		0.512
Hypervascular	8 (14%)	1(ref)		1(ref)	
Rim-enhanced	11 (19.3%)	2.736 [0.723-10.363]	0.138	2.090 [0.067-65.058]	0.674
Hypovascular	38 (66.7%)	7.592 [2.279-25.294]	0.001	5.689 [0.129-250.832]	0.368
Portal vein invasion			0.002		0.077
No	80 (85.1%)	1(ref)		1(ref)	
Yes	14 (14.9%)	2.625 [1.424-4.841]		0.246 [0.052-1.164]	
Microvascular invasion			0.002		0.154
No	45 (45.9%)	1(ref)		1(ref)	
Yes	53 (54.1%)	2.036 [1.289-3.217]		3.336 [0.637-17.466]	
Perineural invasion			0.003		0.269
No	47 (52.8%)	1(ref)		1(ref)	
Yes	42 (47.2%)	2.030 [1.265-3.257]		2.194 [0.545-8.835]	
AJCC T category			0.001		0.335
T1–T2	58 (57.4%)	1(ref)		1(ref)	
T3–T4	43 (42.6%)	2.145 [1.382-3.330]		2.267 [0.430-11.960]	
Morphologic type			0.056		0.450
MF or IG	81 (82.7%)	1(ref)		1(ref)	
Periductal infiltrating	17 (17.3%)	1.636 [0.988-2.710]		1.819 [0.386-8.577]	
Lymph node metastasis			0.001		0.017
No	49 (48.5%)	1(ref)		1(ref)	
Yes	52 (51.5%)	2.136 [1.365-3.344]		4.576 [1.317-15.893]	
RFS < 1yr			<0.001		0.007
No	30 (29.7%)	1(ref)		1(ref)	
Yes	71 (70.3%)	3.584 [2.055-6.251]		8.449 [1.788-39.921]	
Recurrence pattern			<0.001		0.882
Intrahepatic	28 (27.7%)	1(ref)		1(ref)	
Extrahepatic	41 (40.6%)	1.805 [1.026-3.175]	0.040	-	0.929
IH+EH	20 (19.8%)	4.246 [2.215-8.141]	<0.001	1.385 [0.311-6.166]	0.669
Margianl	11 (10.9%)	1.509 [0.682-3.337]	0.310	2.066 [0.351-12.163]	0.423
Treatment type for recurrence					
Supportive care	38 (37.5%)	1 (ref)		1 (ref)	
Surgery	14 (13.9%)	0.461 [0.228-0.930]	0.031	0.005 [0-0.118]	0.001
Chemotherapy	25 (24.8%)	0.830[0.500-1.378]	0.472		
CRRT/RT	13 (12.9%)	0.910 [0.468-1.767]	0.780		
TACE/RFA	11 (10.9%)	0.449 [0.206-0.977]	0.044	2.792 [0.277-28.110]	0.384
Bwt, body weight; *CA 19-9*, Carbohydrate Antigen 19-9; *CT*, computed tomography; *MF*, mass forming; *IG*, intraductal growth; *RFS*, recurrence free survival; *IH*, intrahepatic; *EH*, extrahepatic					

Table S1: Types of treatment modalities according to recurrence patterns (N=101)

Recurrence pattern		No. of patients (No. of patients with OS after recurrence >36 months)					
		Surgery	TACE/RFA	RT/CCRT	Chemotherapy	Supportive	Total
IH	Single	4 (3)	5 (3)	2 (1)	2 (1)	1 (1)	14 (9)
	Multiple	1 (1)	3 (1)	1 (0)	5 (0)	4 (0)	14 (2)
	Subtotal	5 (4)	8 (4)	3 (1)	7 (1)	5 (1)	28 (11)
Marginal	Single					3 (0)	3 (0)
	Multiple		2 (2)		5 (1)	2 (0)	9 (3)
	Subtotal		2 (2)		5 (1)	5 (0)	12 (3)
EH	Single	7 (4)		5 (0)	8 (0)	3 (1)	23 (5)
	Multiple			2 (0)	5 (2)	11 (0)	18 (2)
	Subtotal	7 (4)		7 (0)	13 (2)	14 (1)	41 (7)
IH+EH		2 (0)	1 (0)*	2 (0)*	2 (0)	14 (1)	20 (1)
Total		14 (8)	10 (6)	12 (1)	27 (4)	38 (3)	101 (22)

TACE, transarterial chemoembolization; *RFA*, radiofrequency ablation; *RT*, radiation therapy; *CCRT*, concurrent chemoradiation therapy; *IH*, intrahepatic; *EH*, extrahepatic
* One patient is duplicated between the two treatment subgroups.

5. Discussion

ICC is reportedly associated with lower survival rates than HCC with resectability rates ranging from 58.7% to 78% [19-22]. Nonetheless, even after curative hepatectomy, the recurrence rate is high, and the survival rate remains poor. Previous studies have reported recurrence rates to be approximately 50%–80%, and 5-year survival rates after curative hepatectomy range from 23% to 48% [2,9,11]. This study analyzed ICC recurrence rate, recurrence patterns, RFS and PRS and risk factors in 147 serial ICC patients treated with hepatectomy. The tumor recurred in 101 patients (68.7%) within a median of 12 months (95% CI, 9.9–23.8 months) postoperatively, and the median PRS was found to be 11 months (95% CI, 8.1–16.2 months). The 5-year OS after recurrence was 18%. Compared with our previous study, RFS and PRS were improved in this study despite a slightly higher recurrence rate [11].

In this study, patients with postoperative recurrence were divided into 4 groups, namely IH recurrence, marginal recurrence, EH recurrence, and both IH + EH recurrence. EH recurrence represented the most common recurrence pattern, followed by IH recurrence, both IH + EH recurrence and marginal recurrence, respectively. As reported by previous studies, ICC patients with EH recurrence and both IH + EH recurrence showed unfavorable RFS and PRS. In addition, LN metastasis was significantly associated with these unfavorable recurrence patterns and it was an independent risk factor for poor PRS. Patients with LN metastasis at primary hepatectomy showed shorter RFS than others in the EH ± IH recurrence group. LN metastasis has been one of the strongest predictors of a poor prognosis in patients undergoing surgery for ICC [23-25]. Therefore, the 2020 NCCN guidelines recommend portal lymphadenectomy during surgery for ICC [23]. Lymphadenectomy is necessary for accurate staging of ICC and prediction of postoperative prognosis. Furthermore, it can help establish postoperative follow-up and treatment strategies for patients. However, there are no data to support the oncological effect of routine lymphadenectomy [26]. In this study, out of 15 patients with recurrence at regional LN, LN dissection during primary hepatectomy was conducted in 11 patients. LN metastasis was confirmed in 8 patients after primary hepatectomy, and patients with recurrence at regional LN (n = 15, 7 in LN #12 and 8 in LN #16) showed shortest RFS among the EH recurrences after primary hepatectomy. However, the number of LN harvests and the extent of LN dissection were heterogenous in these patients. Therefore, the extent of LN resection during surgery for ICC should be established through further studies. In the current study, the RFS and PRS of patients with marginal recurrence were better than those of patients with EH ± IH recurrence and worse than those in cases with IH recurrence. In a recently published study by Hu et al., IH recurrence was most common ICC recurrence pattern after primary surgery, and patients with IH marginal recurrence showed shorter DFS and a worse prognosis after recurrence, as opposed to patients with other recurrence patterns; besides, margin status was associated with this unfavorable pattern. Our results were different from those reported by Hu et al, probably due to the differences in treatment strategies. In particular, Hu et al. conducted their study at multiple institutions in various countries with possibly different treatment strategies (e.g., surgical technique, extent of surgery, and indications of adjuvant treatment). On the contrary, the setting of this single-center study eliminated differences in local routines and traditions. In addition, not all cases of ICC recurrence were confirmed, pathologically, as both studies used radiological images or tissue biopsy for diagnosis. Also, the biological and genetic characteristics of ICC patients in this study might have differed from those of ICC patients studied by Hu et al [10].

There are relatively few reports evaluating the treatment of recurrent ICC after hepatic resection [9,29-33]. In a study of 13 patients undergoing repeated surgical resection for recurrent ICC by Kamphues et al. found that the median survival for all patients was 51 (12-69) months, with 1- and 3-year survival rates after primary surgery being 92% and 52%, respectively [30. Sulpice et al. reported on the prognostic effect of repeat hepatectomy and TACE in ICC patients with IH recurrence [31]. Based on their findings, they suggested that repeated resection and other local treatment modalities might improve OS in patients with localized IH recurrence. In the present study, various treatment modalities were used for patients with recurrent ICC. Our results also indicated that use of local treatment modalities (including surgery, TACE, and RFA) to control localized recurrent disease improved PRS, and surgical resection was an independent factor associated with favorable PRS. In patients with EH recurrence, favorable outcomes cannot be expected with local or systemic therapy, which limits the choice of optimal treatment for recurrent disease. However, our study demonstrated that surgical resection for localized EH recurrence offered favorable long-term survival and a durable recurrence-free state. According to the results of this study, locoregional treatment including surgery and TACE/RFA showed more favorable PRS than that in other treatment groups.

The significance of RFS on PRS prognosis is still controversial [34]. A few studies reported early recurrence as an independent risk factor for prognosis of recurrent ICC [35,36]. In this study, long RFS (>1 year) was one of the independent risk factors for favorable PRS and cases with RFS > 1 year reflected the tendency of long-term survival after recurrence. In addition, a few recurrent ICC patients without active treatment after long RFS also showed long-term survival. The length of RFS and PRS may be attributed to the different biological characteristics of ICC.

Accordingly, this study revealed favorable PRS in patients with RFS for > 1 year, whose recurrence was treatable with locoregional treatment, including surgery.

The current study had several limitations. First, as with all retrospective studies, this investigation may have been subject to a selection bias regarding the diagnosis and treatment of patients with recurrent ICC, given that only patients undergoing surgical resection were included in the study. In addition, the number of cases was small despite a study period of >10 years as ICC is a rare disease. Thus, statistical analysis remains a challenge. One approach to overcome this caveat is a multicenter study. We could not compare the efficacy of multimodal and unimodal treatments for recurrent ICC following surgery, and there is no evidence concerning which treatment mode is better. However, it may depend on the individual patient's condition. Thus, further studies are needed to validate various treatment modes. Finally, like other similar studies in the literature, the recurrence of primary cancer was not pathologically confirmed in all cases. Therefore, caution is required when interpreting the results.

6. Conclusion

LN metastasis at primary hepatectomy was associated with unfavorable recurrence patterns (i.e., EH ± IH recurrence) leading to poor PRS. Long-term survivors tended to have longer RFS and locoregional treatment after recurrence. Therefore, local treatment (especially surgery) could be considered if the disease and host conditions are acceptable and tolerable especially in localized, recurrent ICC after long RFS.

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