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Original Research

Prognostic factors in patients with recurrent intrahepatic cholangiocarcinoma after curative resection: A retrospective cohort study

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ABSTRACT

Background: The aim of this study is to determine the outcomes and prognostic factors in patients with recurrent intrahepatic cholangiocarcinoma after curative hepatectomy.

Methods: Clinical, histopathological, and treatment data of 53 patients with recurrent cholangiocarcinoma after curative resection from 2005 to 2015 at our institutes were investigated and analyzed by univariate and multivariate analyses (E-788).

Results: Recurrent cholangiocarcinoma occurred in 53 of 97 patients who underwent curative resection for intrahepatic cholangiocarcinoma. The median overall survival after recurrence was 13.6 months (range, 1–55 months). Multivariate analysis revealed that recurrent treatment without surgery ($p = 0.0007$), gross appearance except for mass-forming type ($p = 0.0183$) and bile duct invasion at the initial surgery ($p = 0.0093$) were significant poor prognostic factors in recurrent cholangiocarcinoma. Median survival of patients after surgical treatment for recurrent cholangiocarcinoma was 36.7 months versus 13.1 months in patients who did not undergo surgery ($p = 0.029$).

Conclusions: Surgical treatment, gross appearance in mass-forming type and the absence of bile duct invasion were independent favorable factors for survival among patients with recurrent cholangiocarcinoma. We recommend surgical treatment for localized recurrence, even if it occurs early after the initial hepatectomy.

1. Introduction

Intrahepatic cholangiocarcinoma (ICC) carries poor prognosis [1]. The possible causative risk factors of ICC are similar to those of hepatocellular carcinoma (HCC), such as cirrhosis, chronic hepatitis B and C, obesity, diabetes, and alcohol consumption [2]. Partial liver resection is the only established therapy to achieve a possible cure in patients with ICC [1]. However, the incidence of recurrence is very high and the 5-year survival rate after partial hepatectomy is only 20–40% [3–6]. The risk factors for ICC recurrence after surgery included multiple tumors, vascular invasion, and lymph node metastasis [1]. Regarding the overall survival of patients with ICC, lymph node metastasis, vascular invasion, multifocal lesions, tumor diameter, old age, and cirrhosis were associated with poor prognosis [3,7,8]. However, limited data are available in patients with recurrent ICC after curative resection.

The aim of this multi-center study was to identify the predictive factors of survival in patients who had recurrent ICC after curative resection.

2. Methods

From January 2005 to December 2015, 97 patients underwent the initial operation for ICC at the following 7 institutions of our study group. The institutional Review Board of each institution approved this

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Table 1
Univariate and multivariate analysis for prognostic factors after recurrent ICC following curative hepatectomy.

Factors	n	Univariate		Multivariate		
		Median survival months after recurrence (95% CI)	p value	HR	95% CI	p value
Age (years)			0.860			
< 70	28	13.3 (8.4–23.0)				
> 70	25	13.7 (7.8–22.7)				
Sex			0.8362			
M	26	13.7 (8.4–23.0)				
F	27	13.3 (7.8–24.1)				
BMI (kg/m2)			0.2514			
< 23	28	14.6 (8.4–22.7)				
> 23	19	13.0 (5.3–17.3)				
HBV			0.5685			
Yes	7	17.3				
no	46	13.7 (10.4–17.0)				
HCV			0.4969			
Yes	8	15.0				
no	45	13.3 (10.4–19.8)				
Recurrence-free survival (years)			0.4645			
< 1	33	13.3 (7.8–19.8)				
> 1	20	13.8 (10.4–36.8)				
Post-operative complications			0.5612			
Yes	11	12.8 (5.3–44.6)				
No	42	13.8 (8.4–22.7)				
Macroscopical findings			0.0211			0.0183
MF	37	16.3 (11.3–24.0)		1		
Others (PI, IG, MF + PI)	16	10.2 (4.0–13.8)		4.01	1.27–13.42	
im			0.3512			
Yes	14	13.3 (4.1–36.8)				
No	35	13.7 (8.4–19.8)				
vp			0.3475			
Yes	27	13.8 (5.3–17.3)				
No	23	13.7 (11.3–36.6)				
vv			0.1129			
Yes	15	8.4 (4.4–13.8)				
No	35	17.0 (11.3–24.1)				
b			0.0221			0.0094
Yes	29	10.6 (5.9–14.8)		4.88	1.45–20.46	
No	18	22.7 (12.8–25.6)		1		
Tumor differentiation			0.3060			
wel, mod	36	13.1 (8.4–16.8)				
por	12	17.3 (4.4–44.6)				
Lymph node metastasis			0.1435			
Yes	11	10.6 (5.9–19.8)				
No	42	14.6 (11.3–23.0)				
CEA (initial)			0.0025			0.4761
< 5 ng/ml	35	17.3 (13.1–24.2)		1		
> 5 ng/ml	16	7.8 (4.4–14.8)		1.74	0.37–8.41	
CEA (at recurrence)			0.0024			0.9507
< 5 ng/ml	34	22.7 (13.0–36.6)		1		
> 5 ng/ml	14	8.4 (4.4–14.8)		1.05	0.23–4.24	
CA19-9 (initial)			< 0.0001			0.3939
< 40 U/ml	27	24.2 (16.4–36.8)		1		
> 40 U/ml	23	10.6 (7.2–13.0)		2.46	0.30–20.18	
CA19-9 (at recurrence)			< 0.0001			0.2097
< 40 U/ml	30	23.0 (16.4–36.6)		1		
> 40 U/ml	18	8.4 (5.3–11.3)		3.52	0.50–32.09	
GPS (initial)			0.2541			
0	39	14.6 (12.8–23.0)				
1	13	8.4 (4.4–22.7)				
GPS (at recurrence)			0.0023			0.8886
0	33	17.3 (13.0–25.6)		1		
1,2	11	7.8 (1.0–14.6)		1.16	0.14–9.48	
NLR (initial)			0.0040			0.6640
< 1.6	15	7.8 (3.4–13.7)		1.34	0.33–4.93	
> 1.6	36	17.0 (12.8–24.2)		1		
NLR (at recurrence)			0.5579			
< 2.1	24	13.8 (11.3–36.6)				
> 2.1	23	13.3 (8.4–22.7)				
PNI (initial)			0.0599			
< 45	10	8.2 (0.7–13.7)				
> 45	41	14.8 (12.8–24.1)				
PNI (at recurrence)			0.0043			0.5952
< 45	15	10.4 (3.8–13.3)		1.56	0.27–7.50	
> 45	30	17.3 (13.0–25.6)		1		

(*continued on next page*)

Table 1 (*continued*)

Factors	n	Univariate		Multivariate		
		Median survival months after recurrence (95% CI)	p value	HR	95% CI	p value
Tumor size (initial)			0.8171			
< 3 cm	19	14.6 (7.8–24.2)				
> 3 cm	34	13.3 (8.4–22.7)				
Tumor size (at recurrence)			0.1189			
< 2 cm	29	16.4 (10.6–25.6)				
> 2 cm	22	13.1 (7.8–17.3)				
Tumor number (initial)			0.1238			
solitary	43	13.1 (8.4–17.0)				
multiple	10	19.8 (4.1–54.6)				
Tumor number (at recurrence)			0.4670			
solitary	20	13.0 (5.9–24.1)				
multiple	32	14.6 (10.4–23.0)				
Adjuvant therapy			0.9314			
Yes	17	13.1 (8.4–19.8)				
No	35	14.8 (7.2–23.0)				
Extrahepatic metastasis			0.0127			0.3706
Yes	31	13.0 (8.4–14.8)		1.93	0.47–9.36	
No	22	23.0 (7.8–54.6)		1		
Surgical treatment for recurrence			0.0306			0.0007
Yes	6	36.8		1		
No	46	13.3 (8.4–17.0)		44.9	4.02–1410.17	

b, bile duct invasion; BMI, body mass index; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; GPS, Glasgow Prognostic Score; HBV, hepatitis B; HCC, hepatocellular carcinoma; HCV, hepatitis C; HR, hazard ratio; im, intrahepatic metastasis; MF, mass-forming type; NLR, neutrophil-to-lymphocyte ratio; PNI, prognostic nutritional index; vp, portal vein invasion; vv, hepatic vein invasion.

study (E-788). Among 97 patients who had curative hepatectomy for ICC, fifty-three (54.6%) patients had recurrent ICC. The baseline characteristics and clinicopathologic features of these patients are shown in Table 1. A radiological diagnosis was made of mass-forming (MF) type in 37 patients, periductal infiltrative (PI) type in 2 patients, intraductal growth (IG) type in 1 patient, and MF + PI type in 13 patients, as classified according to the Liver Cancer Study Group of Japan [9].

All patients underwent hepatectomy and the choice of resection was based on the tumor size, tumor location, preoperative diagnosis, and liver function. Lymph node dissection was not performed uniformly in all patients because of the multicenter retrospective nature of the study. Of the 97 patients, 23 patients (23.7%) underwent lymph node dissection.

All the patients were followed up after surgery for a median of 28.8 months (range, 1–127 months), and recurrence was determined by imaging with abdominal computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography-CT (PET-CT), or biopsy. In cases of solitary ICC recurrence in the liver or lung, tumor resection or radiofrequency ablation (only for liver) was performed when the surgeons decided that tumor resection was possible based on the size, position of tumors, and patient condition including performance status and liver function reserve. When recurrence included multiple tumors in the liver and/or other organs including lymph nodes, chemotherapy (systemic or transarterial chemoembolization) or radiation therapy was performed, or the best supportive care was provided.

Data were collected and analyzed with JMP Pro 12 statistical software (SAS Institute Inc., NC, USA). For selection of optimal cut-off values to predict the overall survival after ICC recurrence, receiver operating characteristic (ROC) analysis was used. Survival analysis and survival plots were performed with the Kaplan-Meier method and the log rank test was applied where appropriate to verify the statistical significance of differences. To identify the factors influencing survival factors and their hazard ratios (HRs), the parameters were analyzed by univariate and risk-adjusted multivariate Cox-regression analyses. Variables entered in these analyses were age, gender, body mass index (BMI), hepatitis B (HBV) and hepatitis C (HCV) statuses, recurrent-free survival, post-operative complications, intrahepatic metastasis (im), portal vein invasion (vp), hepatic vein invasion (vv), bile duct invasion (b), tumor differentiation, lymph node metastasis, carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) levels, Glasgow Prognostic Score (GPS) [10], neutrophil-to-lymphocyte ratio (NLR) [11], prognostic nutritional index (PNI) [12], gross appearance (MF or others including PI, IG, MF + PI), tumor size, tumor number, adjuvant therapy, extrahepatic metastasis, and surgical treatment for recurrence. The work has been reported in line with the STROCSS criteria [13].

3. Results

The overall survival of our study population was 97%, 55%, and 47% after 1, 3, and 5 years, respectively. The disease free survival was 65%, 48%, and 42% after 1, 3, and 5 years, respectively. With a median follow-up period of 28.8 months, recurrence occurred in 53 (54.6%) of the 97 patients with ICC who underwent curative hepatectomy. The median period from surgery to recurrence was 9.9 months (range, 0–105 months). Sixty-two percent of patients experienced recurrence within 1 year after the surgery (Fig. 1A). Early recurrence within 1 year after the initial surgery had no effect on mortality after recurrence (Fig. 1B). The median survival time after recurrence was 13.6 months (range, 1–55 months). After recurrence, the survival rates were 61.4% and 22.1% at 1 and 3 years, respectively (Fig. 2).

Table 1 shows the prognostic factors for survival in patients with ICC recurrence. Univariate analysis showed that the following 11 factors are significant: gross appearance including PI, IG, and MF + PI type, bile duct invasion, CEA > 5 ng/ml, CA19-9 > 40 U/ml, NLR < 1.6 at the initial surgery, extra hepatic metastasis, CEA > 5 ng/ml, CA19-9 > 40 U/ml, GPS 1 or 2, PNI less than 45 at recurrence, and treatment methods except for surgery at recurrence. Multivariate analysis showed only three factors to be independently significant: treatment methods except for surgery at recurrence ($p = 0.0007$), gross appearance including PI, IG, and MF + PI type ($p = 0.0183$) and bile duct invasion in the initial pathology ($p = 0.0093$).

Six patients underwent surgical treatment for recurrence (Table 2), 37 patients underwent chemotherapy, and 10 patients underwent palliative treatment, depending on their respective condition or tumor spread at the time of recurrence. Four of 6 patients who underwent surgical resection achieved complete cure after the surgery; however,

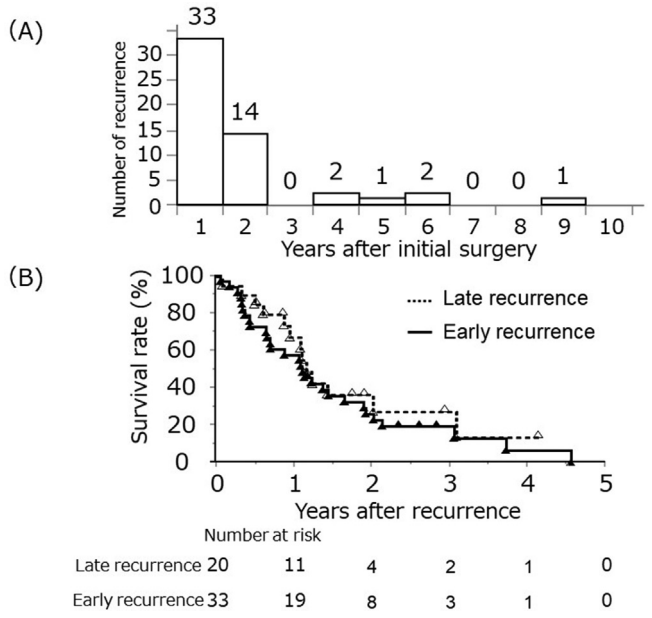

Fig. 1. (A) Numbers of patients who had recurrent cholangiocarcinoma after curative hepatectomy for ICC. X-axis indicates years after the initial surgery. (B) Survival curves of patients with recurrent ICC between early recurrence (within 1 year) and late recurrence (after 1 year).

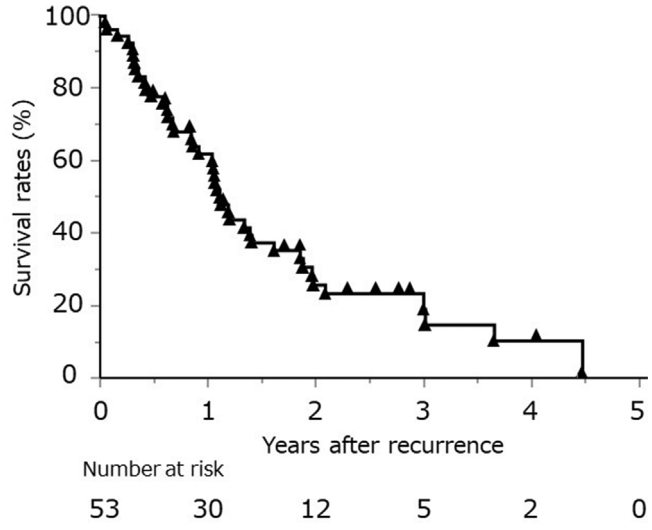

Fig. 2. Survival curves of patients with recurrent ICC.

the two other patients had re-recurrence after surgery for metastasis. Four patients with intrahepatic recurrence underwent hepatectomy, whereas the patients with extrahepatic recurrence underwent lung wedge resection. In case 3 patient, he received radiation therapy for bone metastasis 14 months after VATS for lung metastasis. In spite of chemotherapy of gemcitabine and TS-1, he died from original disease 37 months after surgery for metastasis. Five patients had MF type and the other patient had PI type in gross appearance. Regarding adjuvant chemotherapy, three of 6 patients received adjuvant chemotherapy using gemcitabine + TS-1 after initial surgery. After surgery for metastasis, three of 6 patients received adjuvant chemotherapy. The median survival duration of patients undergoing surgical treatment for ICC recurrence was 36.7 months versus 13.1 months in patients who did not undergo surgery (p = 0.029; Fig. 3).

Table 2
Characteristics of surgical treatment for recurrent ICC.

No	Age	Sex	Macroscopic type	Max tumor size (mm)	Tumor number	Histology	Vascular invasion	Lymph node metastasis	Adjuvant chemotherapy after initial surgery	Recurrent tumor size (mm)	Recurrence site	Operative methods	Adjuvant chemotherapy after surgery for metastasis	Time to recurrence after initial surgery (months)	Survival after recurrence (months)	Outcome
1	40	M	MF	20	1	mod	P	A	none	7	Lung	partial resection	none	44.4	34.8	NED
2	65	M	MF	21	1	mod	P	A	none	26	Liver	partial resection	IFN	3.6	3.6	DFD
3	64	M	MF	20	1	mod	P	A	GEM + S1	13	Lung	partial resection	none	64.8	37.2	DFD
4	67	M	MF	34	1	wel	P	A	GEM + S1	20	Liver	anterior sectionectomy	GEM + S1	61.2	21.6	NED
5	70	F	MF	24	2	mod	A	A	none	11	Liver	partial resection	GEM + S1	19.2	49.2	NED
6	69	F	PI	30	5	mod	P	A	GEM + S1	13	Liver	partial resection	none	15.6	10.8	NED

MF, the mass-forming type; PI, the periductal infiltration type; mod, moderately differentiated adenocarcinoma; wel, well differentiated adenocarcinoma; P, present; A, absent; GEM, gemcitabine; S1, TS-1; NED, no evidence of disease; DFD, died from disease.

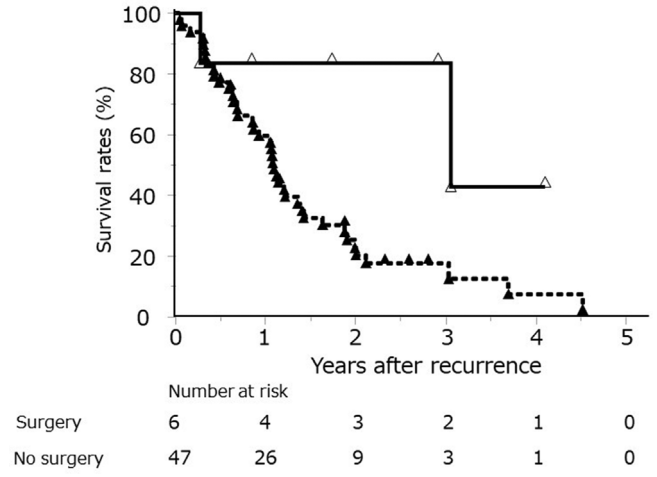

Fig. 3. Patients with recurrent ICC who received surgical treatment had a significantly better long-term survival after recurrence than those who did not (Log rank = 0.0029).

4. Discussion

In this study, we have shown that the favorable factors in patients with recurrent ICC after curative resection were surgical treatment at recurrence, gross appearance in MF type, and the absence of bile duct invasion in the initial pathology. The median survival time of 6 patients who underwent surgical resection for ICC recurrence was 36.7 months after recurrence.

The overall survival in patients who underwent surgical resection for ICC recurrence was significantly better than that of patients who did not undergo surgery. Previous reports have shown that the remnant liver is the most common site of recurrence [14]. Surgical resection was the best treatment option if the patient condition was favorable. Several studies showed the efficacy of surgical resection for ICC recurrence as an independent prognostic factor [15–17]. The median survival time after surgical resection for ICC recurrence varies from 18.9 to 45.1 months (Table 3) [15–22]. Other case studies have advocated a survival benefit of repeated surgical resection including lung resection for ICC recurrence [23–29]. In addition to surgery, multimodal management including radiofrequency ablation and radiotherapy might result in significant prolongation of survival. Median survival times of RFA and radiotherapy were 9.6–51 months and 13 months, respectively [5,17,30–32].

Bile duct invasion is also one of the poor prognostic factors for ICC surgery. Bile duct invasion tended to increase the perihilar or systemic recurrence. In this cohort, bile duct invasion was not correlated with un-resectable recurrence or early recurrence. Regarding gross appearance of ICC, MF type was related with intrahepatic recurrence after surgery for ICC [29]. Miwa et al. reported that MF + PI type was a risk factor for poorer survival after ICC hepatectomy [33]. Previous studies have identified prognostic factors after surgery for ICC, such as tumor size, vascular and serosal invasion, age at diagnosis, number of tumors, cirrhosis of the liver, intrahepatic metastasis, preoperative CA19-9 levels, lymph node metastasis, histological grade, and remnant cancer after surgery [7,29,34–41]. Regarding the prognostic factors after recurrent ICC, we have identified the prognostic factors including surgical resection, gross appearance in MF type and the absence of bile duct invasion at initial pathology. Table 3 summarizes the prognostic factors after recurrent ICC from previous studies. The lymph node metastasis is considered as one of the most important prognostic factors in ICC. However; lymph node metastasis did not affect the prognosis after ICC recurrence in this cohort.

In this study, the recurrence rate of cholangiocarcinoma was 54.6%, and about 62% of recurrences occurred within 1 year (Fig. 1A). Recent studies reported that the time to recurrence of less than 1 year was a prognostic factor after ICC recurrence [19,20]. Some immunohistochemical markers including pancreatic secretory trypsin inhibitor (PSTI) and insulin-like growth factor-II mRNA-binding protein 3 (IMP3) were reported as predictive factors for early recurrence of ICC after surgery [42,43]. In the current study, the rate of solitary intrahepatic recurrent ICC was indeed significantly lower in the early recurrence group compared with in the late recurrence group (6.1% vs 35.0%; p = 0.007, data not shown). However, early recurrence within 1 year after the initial surgery had no effect on mortality after recurrence (Fig. 1B). Therefore, surgical treatment should be considered in cases of localized recurrence even if it occurred early after the initial hepatectomy.

This study had several limitations. First, this is a retrospective cohort study resulting in selection and detection bias. In addition, this study included a small number of patients who underwent surgical resection for recurrent ICC. Second, medical records of all the patients could not be assessed, which reduced the number of study subjects. Although there are several limitations, our results from multicenter study might be useful for treatment strategies of ICC recurrence. Further prospective, national multicenter studies should be planned to

Table 3
Surgical treatment for recurrent ICC.

No	Author	Year	Number	MST after recurrence (months)	1 year survival after rec (%)	3 years survival after rec (%)	Prognostic factors after ICC recurrence
1	Song [13]	2011	27	18.9	–	–	Surgical resection
2	Sulpice [15]	2012	4	–	100	100	Repeat hepatectomy Intra-arterial yttrium-90 radiotherapy
3	Hyder [16]	2013	33	25.8	–	–	–
4	Zhang [20] >	2013	32	20.3	83.8	17.1	Recurrence interval Tumor number of recurrence
5	Park [20]	2016	12	21.0	–	–	Bile duct invasion Disease-free survival time shorter than 1 year
6	Souche [14]	2016	10	25.0	–	–	Repeat hepatectomy
7	Spolverato [19]	2016	41	26.1	–	–	–
8	Si [18]	2017	72	45.1	97.2	67	CA19-9 > 39U/ml Recurrent tumor > 3 cm Multiple recurrent tumors Time to recurrence < 1 year
9	this study	–	6	36.7	83.3	83.3	Surgical resection Gross appearance MF type Bile duct invasion

CA19-9, carbohydrate antigen 19-9; MF, mass-forming; MST, median survival time; rec, recurrence.

overcome these limitations.

In conclusion, surgical treatment, gross appearance in MF type and bile duct invasion were independent factors for the survival of patients with recurrent ICC. We recommend surgical treatment for localized recurrences, even if they occur early after the initial hepatectomy.

Ethical approval

The institutional Review Board of each institution approved this study (E-788).

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Author contribution

MO; study design, data collection, statistics, write manuscript.
TK; study design.
MH; data collection.
HT; data collection.
TA; data collection.
AO; data collection.
TK; data collection.
TI; data collection.
KO; data collection.
HO; study design.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Research registration number

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Guarantor

Masahiro Ohira.

References

[1] J. Bridgewater, P.R. Galle, S.A. Khan, J.M. Llovet, J.W. Park, T. Patel, T.M. Pawlik, G.J. Gores, Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma, J. Hepatol. 60 (2014) 1268–1289.

[2] W.C. Palmer, T. Patel, Are common factors involved in the pathogenesis of primary liver cancers? A meta-analysis of risk factors for intrahepatic cholangiocarcinoma, J. Hepatol. 57 (2012) 69–76.

[3] M.C. de Jong, H. Nathan, G.C. Sotiropoulos, A. Paul, S. Alexandrescu, H. Marques, C. Pulitano, E. Barroso, B.M. Clary, L. Aldrighetti, C.R. Ferrone, A.X. Zhu, T.W. Bauer, D.M. Walters, T.C. Gamblin, K.T. Nguyen, R. Turley, I. Popescu, C. Hubert, S. Meyer, R.D. Schulick, M.A. Choti, J.F. Gigot, G. Mentha, T.M. Pawlik, Intrahepatic cholangiocarcinoma: an international multi-institutional analysis of prognostic factors and lymph node assessment, J. Clin. Oncol. 29 (2011) 3140–3145.

[4] K. Uchiyama, M. Yamamoto, H. Yamaue, S. Ariizumi, T. Aoki, N. Kokudo, T. Ebata, M. Nagino, M. Ohtsuka, M. Miyazaki, E. Tanaka, S. Kondo, T. Uenishi, S. Kubo, H. Yoshida, M. Unno, S. Imura, M. Shimada, M. Ueno, T. Takada, Impact of nodal involvement on surgical outcomes of intrahepatic cholangiocarcinoma: a multicenter analysis by the Study Group for Hepatic Surgery of the Japanese Society of Hepato-Biliary-Pancreatic Surgery, J. Hepato-Biliary-Pancreatic Sci. 18 (2011) 443–452.

[5] G. Ercolani, G. Vetrone, G.L. Grazi, O. Aramaki, M. Cescon, M. Ravaioli, C. Serra, G. Brandi, A.D. Pinna, Intrahepatic cholangiocarcinoma: primary liver resection and aggressive multimodal treatment of recurrence significantly prolong survival, Ann. Surg. 252 (2010) 107–114.

[6] Q. Wang, J. Li, Z. Lei, D. Wu, A. Si, K. Wang, Y. Wang, X. Wan, W.Y. Lau, F. Shen, Prognosis of intrahepatic cholangiocarcinomas with HBV infection is better than those with hepatolithiasis after R0 liver resection: a propensity Score matching analysis, Ann. Surg Oncol. 24 (2017) 1579–1587.

[7] O. Hyder, H. Marques, C. Pulitano, J.W. Marsh, S. Alexandrescu, T.W. Bauer, T.C. Gamblin, G.C. Sotiropoulos, A. Paul, E. Barroso, B.M. Clary, L. Aldrighetti, C.R. Ferrone, A.X. Zhu, I. Popescu, J.F. Gigot, G. Mentha, S. Feng, T.M. Pawlik, A nomogram to predict long-term survival after resection for intrahepatic cholangiocarcinoma: an Eastern and Western experience, JAMA Surg. 149 (2014) 432–438.

[8] G. Nuzzo, F. Giuliante, F. Ardito, I. Giovannini, L. Aldrighetti, G. Belli, F. Bresadola, F. Calise, R. Dalla Valle, D.F. D'Amico, L. Gennari, S.M. Giulini, A. Guglielmi, E. Jovine, R. Pellicci, H. Pernthaler, A.D. Pinna, S. Puleo, G. Torzilli, L. Capussotti, A. Italian Chapter of the International Hepato-Pancreato-Biliary, U. Cillo, G. Ercolani, M. Ferrucci, L. Mastrangelo, N. Portolani, C. Pulitano, D. Ribero, A. Ruzzenente, V. Scuderi, B. Federico, Improvement in perioperative and long-term outcome after surgical treatment of hilar cholangiocarcinoma: results of an Italian multicenter analysis of 440 patients, Arch. Surg. 147 (2012) 26–34.

[9] Liver Cancer Study Group of Japan, General Rules for the Clinical and Pathological Study of Primary Liver Cancer, 5th Japanese edition, Kanehara, Tokyo, 2008.

[10] T. Abe, H. Tashiro, M. Hattori, S. Kuroda, H. Tahara, M. Ohira, T. Kobayashi, K. Ide, K. Ishiyama, H. Ohdan, Prediction of long-term survival by using the Glasgow Prognostic Score in patients with hepatocellular carcinoma after liver transplantation, Hepatol. Res. 46 (2016) 622–633.

[11] W. Sr, E.J. Cook, F. Goulder, T.A. Justin, N.J. Keeling, Neutrophil-lymphocyte ratio as a prognostic factor in colorectal cancer, J. Surg. Oncol. 91 (2005) 181–184.

[12] G.P. Buzby, J.L. Mullen, D.C. Matthews, C.L. Hobbs, E.F. Rosato, Prognostic nutritional index in gastrointestinal surgery, Am. J. Surg. 139 (1980) 160–167.

[13] R.A. Agha, M.R. Borrelli, M. Vella-Baldacchino, R. Thavayogan, D.P. Orgill, S. Group, The STROCSS statement: strengthening the reporting of cohort studies in surgery, Int. J. Surg. 46 (2017) 198–202.

[14] I. Endo, M. Gonen, A.C. Yopp, K.M. Dalal, Q. Zhou, D. Klimstra, M. D'Angelica, R.P. DeMatteo, Y. Fong, L. Schwartz, N. Kemeny, E. O'Reilly, G.K. Abou-Alfa, H. Shimada, L.H. Blumgart, W.R. Jarnagin, Intrahepatic cholangiocarcinoma: rising frequency, improved survival, and determinants of outcome after resection, Ann. Surg. 248 (2008) 84–96.

[15] S.C. Song, J.S. Heo, D.W. Choi, S.H. Choi, W.S. Kim, M.J. Kim, Survival benefits of surgical resection in recurrent cholangiocarcinoma, J. Korean Surg. Soc. 81 (2011) 187–194.

[16] R. Souche, P. Addeo, E. Oussoultzoglou, A. Herrero, E. Rosso, F. Navarro, J.M. Fabre, P. Bachellier, First and repeat liver resection for primary and recurrent intrahepatic cholangiocarcinoma, Am. J. Surg. 212 (2016) 221–229.

[17] L. Sulpice, M. Rayar, E. Boucher, M. Pracht, B. Meunier, K. Boudjema, Treatment of recurrent intrahepatic cholangiocarcinoma, Br. J. Surg. 99 (2012) 1711–1717.

[18] O. Hyder, I. Hatzaras, G.C. Sotiropoulos, A. Paul, S. Alexandrescu, H. Marques, C. Pulitano, E. Barroso, B.M. Clary, L. Aldrighetti, C.R. Ferrone, A.X. Zhu, T.W. Bauer, D.M. Walters, R. Groeschl, T.C. Gamblin, J.W. Marsh, K.T. Nguyen, R. Turley, I. Popescu, C. Hubert, S. Meyer, M.A. Choti, J.F. Gigot, G. Mentha, T.M. Pawlik, Recurrence after operative management of intrahepatic cholangiocarcinoma, Surgery 153 (2013) 811–818.

[19] H.M. Park, S.P. Yun, E.C. Lee, S.D. Lee, S.S. Han, S.H. Kim, S.J. Park, Outcomes for patients with recurrent intrahepatic cholangiocarcinoma after surgery, Ann. Surg Oncol. 23 (2016) 4392–4400.

[20] A. Si, J. Li, X. Xing, Z. Lei, Y. Xia, Z. Yan, K. Wang, L. Shi, F. Shen, Effectiveness of repeat hepatic resection for patients with recurrent intrahepatic cholangiocarcinoma: factors associated with long-term outcomes, Surgery 161 (2017) 897–908.

[21] G. Spolverato, Y. Kim, S. Alexandrescu, H.P. Marques, J. Lamelas, L. Aldrighetti, T. Clark Gamblin, S.K. Maithel, C. Pulitano, T.W. Bauer, F. Shen, G.A. Poultsides, T.B. Tran, J. Wallis Marsh, T.M. Pawlik, Management and outcomes of patients with recurrent intrahepatic cholangiocarcinoma following previous curative-intent surgical resection, Ann. Surg Oncol. 23 (2016) 235–243.

[22] S.J. Zhang, P. Hu, N. Wang, Q. Shen, A.X. Sun, M. Kuang, G.J. Qian, Thermal ablation versus repeated hepatic resection for recurrent intrahepatic cholangiocarcinoma, Ann. Surg Oncol. 20 (2013) 3596–3602.

[23] D. Cherqui, B. Tantawi, R. Alon, P. Piedbois, A. Rahmouni, D. Dhumeaux, M. Julien, P.L. Fagniez, Intrahepatic cholangiocarcinoma. results of aggressive surgical management, Arch. Surg. 130 (1995) 1073–1078.

[24] M.M. Konstadoulakis, S. Roayaie, I.P. Gomatos, D. Labow, M.I. Fiel, C.M. Miller, M.E. Schwartz, Fifteen-year, single-center experience with the surgical management of intrahepatic cholangiocarcinoma: operative results and long-term outcome, Surgery 143 (2008) 366–374.

[25] A. Saiura, J. Yamamoto, N. Kokudo, R. Koga, M. Seki, N. Hiki, K. Yamada, T. Natori, T. Yamaguchi, Intrahepatic cholangiocarcinoma: analysis of 44 consecutive resected cases including 5 cases with repeat resections, Am. J. Surg. 201 (2011) 203–208.

[26] G.C. Sotiropoulos, H. Lang, C.E. Broelsch, Surgical management of recurrent intrahepatic cholangiocellular carcinoma after liver resection, Surgery 137 (2005) 669–670.

[27] S. Suzuki, T. Sakaguchi, Y. Yokoi, K. Okamoto, K. Kurachi, Y. Tsuchiya, T. Okumura, H. Konno, S. Baba, S. Nakamura, Clinicopathological prognostic factors and impact of surgical treatment of mass-forming intrahepatic cholangiocarcinoma, World J. Surg. 26 (2002) 687–693.

[28] S.M. Weber, W.R. Jarnagin, D. Klimstra, R.P. DeMatteo, Y. Fong, L.H. Blumgart, Intrahepatic cholangiocarcinoma: resectability, recurrence pattern, and outcomes, J. Am. Coll. Surg. 193 (2001) 384–391.

[29] M. Yamamoto, K. Takasaki, T. Otsubo, H. Katsuragawa, S. Katagiri, Recurrence after surgical resection of intrahepatic cholangiocarcinoma, J. Hepato-Biliary-Pancreatic Surg. 8 (2001) 154–157.

[30] C. Kamphues, D. Seehofer, R.M. Eisele, T. Denecke, J. Pratschke, U.P. Neumann, P. Neuhaus, Recurrent intrahepatic cholangiocarcinoma: single-center experience using repeated hepatectomy and radiofrequency ablation, J. Hepato-Biliary-Pancreatic Sci. 17 (2010) 509–515.

[31] D.H. Jung, M.S. Kim, C.K. Cho, H.J. Yoo, W.I. Jang, Y.S. Seo, E.K. Paik, K.B. Kim,

C.J. Han, S.B. Kim, Outcomes of stereotactic body radiotherapy for unresectable primary or recurrent cholangiocarcinoma, Radiat. Oncol. J 32 (2014) 163–169.
[32] Y. Fu, W. Yang, W. Wu, K. Yan, B.C. Xing, M.H. Chen, Radiofrequency ablation for postoperative recurrences of intrahepatic cholangiocarcinoma, Chin. J. Canc. Res. 23 (2011) 295–300.
[33] S. Miwa, S. Miyagawa, A. Kobayashi, Y. Akahane, T. Nakata, M. Mihara, K. Kusama, J. Soeda, S. Ogawa, Predictive factors for intrahepatic cholangiocarcinoma recurrence in the liver following surgery, J. Gastroenterol. 41 (2006) 893–900.
[34] Y. Wang, J. Li, Y. Xia, R. Gong, K. Wang, Z. Yan, X. Wan, G. Liu, D. Wu, L. Shi, W. Lau, M. Wu, F. Shen, Prognostic nomogram for intrahepatic cholangiocarcinoma after partial hepatectomy, J. Clin. Oncol. 31 (2013) 1188–1195.
[35] S. Marubashi, K. Gotoh, H. Takahashi, H. Ohigashi, M. Yano, O. Ishikawa, M. Sakon, Prediction of the postoperative prognosis of intrahepatic cholangiocarcinoma (ICC): importance of preoperatively- determined anatomic invasion level and number of tumors, Dig. Dis. Sci. 59 (2014) 201–213.
[36] S. Jonas, A. Thelen, C. Benckert, W. Biskup, U. Neumann, B. Rudolph, E. Lopez-Haanninen, P. Neuhaus, Extended liver resection for intrahepatic cholangiocarcinoma: a comparison of the prognostic accuracy of the fifth and sixth editions of the TNM classification, Ann. Surg. 249 (2009) 303–309.
[37] S. Yamasaki, Intrahepatic cholangiocarcinoma: macroscopic type and stage classification, J. Hepato-Biliary-Pancreatic Surg. 10 (2003) 288–291.
[38] M. Shimada, Y. Yamashita, S. Aishima, K. Shirabe, K. Takenaka, K. Sugimachi, Value of lymph node dissection during resection of intrahepatic cholangiocarcinoma, Br. J. Surg. 88 (2001) 1463–1466.
[39] S.B. Choi, K.S. Kim, J.Y. Choi, S.W. Park, J.S. Choi, W.J. Lee, J.B. Chung, The prognosis and survival outcome of intrahepatic cholangiocarcinoma following surgical resection: association of lymph node metastasis and lymph node dissection with survival, Ann. Surg Oncol. 16 (2009) 3048–3056.
[40] Y. Yamashita, A. Taketomi, K. Morita, T. Fukuhara, S. Ueda, K. Sanefuji, T. Iguchi, H. Kayashima, K. Sugimachi, Y. Maehara, The impact of surgical treatment and poor prognostic factors for patients with intrahepatic cholangiocarcinoma: retrospective analysis of 60 patients, Anticancer Res. 28 (2008) 2353–2359.
[41] K. Shirabe, Y. Mano, A. Taketomi, Y. Soejima, H. Uchiyama, S. Aishima, H. Kayashima, M. Ninomiya, Y. Maehara, Clinicopathological prognostic factors after hepatectomy for patients with mass-forming type intrahepatic cholangiocarcinoma: relevance of the lymphatic invasion index, Ann. Surg Oncol. 17 (2010) 1816–1822.
[42] Y.L. Chen, Y.M. Jeng, H.C. Hsu, H.S. Lai, P.H. Lee, P.L. Lai, R.H. Yuan, Expression of insulin-like growth factor II mRNA-binding protein 3 predicts early recurrence and poor prognosis in intrahepatic cholangiocarcinoma, Int. J. Surg. 11 (2013) 85–91.
[43] A. Tonouchi, M. Ohtsuka, H. Ito, F. Kimura, H. Shimizu, M. Kato, Y. Nimura, K. Iwase, T. Hiwasa, N. Seki, M. Takiguchi, M. Miyazaki, Relationship between pancreatic secretory trypsin inhibitor and early recurrence of intrahepatic cholangiocarcinoma following surgical resection, Am. J. Gastroenterol. 101 (2006) 1601–1610.