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Intrahepatic Cholangiocarcinoma With Neither Intrahepatic Metastasis Nor Lymph Node Metastasis Is the Optimal Indication for Hepatectomy With Adjuvant Therapy

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Abstract. *Background/Aim: The optimal indication of hepatectomy with adjuvant therapy for intrahepatic cholangiocarcinoma (ICC) has not been evaluated in detail. Patients and Methods: We retrospectively studied 224 patients with ICC who underwent hepatectomy between 2000 and 2019. Prognostic factors for overall survival (OS) were evaluated by univariate and multivariate analysis. A total of 127 patients were treated with adjuvant therapy (62 patients with chemotherapy and 65 patients with immunotherapy) after hepatectomy, and 97 patients were treated with hepatectomy alone. Results: Intrahepatic metastasis (IM), lymph node metastasis (LNM) of ICC, adjuvant chemotherapy, and adjuvant immunotherapy were significant prognostic factors for OS on multivariate analysis. In 127 patients with neither IM nor LNM, the 5-year OS rate was significantly higher in 36 patients with adjuvant chemotherapy (81%) and in 34 patients with adjuvant immunotherapy (68%) than in 57 patients with hepatectomy alone (45%). Conclusion: The absence of IM or LNM is the optimal indication for hepatectomy with adjuvant therapy in patients with ICC.*

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver cancer, and its incidence is increasing (1-3). Curative surgery is the most effective treatment. However, the rate of recurrence after curative surgery is particularly high, and the 5-year survival rates have been reported to be approximately 20-40% in patients with ICC (4-12). Recently, adjuvant therapy after hepatectomy have been reported in patients with ICC (13, 14). However, the optimal indication of hepatectomy and adjuvant therapy after hepatectomy for ICC has not been evaluated in detail. We attempted to clarify the optimal indications for hepatectomy and adjuvant therapy in patients with ICC.

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Key Words: Intrahepatic cholangiocarcinoma, hepatectomy, curative surgery, adjuvant treatment.

Patients and Methods

Patients. A total of 264 patients with ICC who underwent hepatectomy between 2000 and 2019 at Tokyo Women's Medical University were studied retrospectively. Prognostic factors for survival were evaluated by univariate and multivariate analysis. Fifteen patients with intraductal growth (IG) type, 22 patients who underwent non-curative hepatectomy, and 3 patients with in-hospital death were excluded. This study was approved by the Committee of Medical Ethics of Tokyo Women's Medical University.

Surgery. All patients underwent hepatectomy, and the choice of hepatic resection was made on the basis of the tumor location (periphery or perihilar) and macroscopic tumor type [mass-forming (MF) type, periductal infiltrating (PI) type, and MF+PI type] (15). In most patients with MF type ICC at the periphery of the liver, anatomical hepatectomy such as hemihepatectomy or sectionectomy was performed considering functional liver reserve (16). In patients with MF type in whom lymph node metastasis (LNM) was suspected intraoperatively, lymph node dissection (around the hepatoduodenal ligament, posterior to the upper portion of the pancreas head, and along the common hepatic artery) was performed (16). However, in patients with MF type ICC with liver cirrhosis, only hepatectomy without lymph node dissection was performed (16). In patients with PI type and MF+PI type of ICC, which was located in and invaded the perihilar portion, hemihepatectomy with extrahepatic bile duct resection and lymph node dissection were performed (16).

Adjuvant therapy. As an adjuvant therapy, 65 patients were treated with immunotherapy from 2000. Each patient signed informed consent and agreed to receive immunotherapy [the Dendritic cells (DC) vaccine plus cytotoxic activated T-cell (CAT) transfer] before hepatectomy (17). Fresh frozen tumor sample was taken for DC vaccine at hepatectomy. A total of 3 DC vaccinations plus CAT transfer were performed within 2 months after hepatectomy. From 2007, 62 patients were treated with chemotherapy with S-1 (tegafur with gimeracil) because the Japanese national insurance system allowed S-1 for patients with biliary tract cancer and ICC. S-1 was started within 2-3 months after hepatectomy. S-1 was given orally at a dose of 40-80 mg per day for 2 weeks and no chemotherapy was given for the following 2 weeks. S-1 chemotherapy was continued until recurrence of ICC; therefore, the duration of chemotherapy with S-1 was between 6 months and 5 years. Ninety-seven patients were treated with hepatectomy alone because of the following reasons; preoperative diagnosis of HCC with cirrhosis (n=31), no request for adjuvant therapy (n=20), immediate recurrence after hepatectomy (n=16), difficulty to come to the hospital (n=12), other disease (n=7), old age (n=5), hemodialysis (n=2), preoperative diagnosis of colorectal liver metastasis (n=1), and severe morbidity after hepatectomy (n=3).

Pathological findings. Macroscopic tumor type and pathological findings were examined according to the General Rules for the Clinical and Pathological Study of Primary Liver Cancer of the Liver Cancer Study Group of Japan (LCSGJ) (15). The terminology of hepatectomy was determined based on the Terminology Committee of the International Hepato-Pancreato-Biliary Association in 2000 (18).

Follow-up. After hepatectomy, patients were followed up every 4-12 weeks at the outpatient department of our institution. Ultrasonography or computed tomography was performed once every 3-4 months. Overall survival (OS) was defined from the time of surgery to the time of ICC-related death, or last follow-up. Recurrence-free survival (RFS) was defined from the time of surgery to the time of radiological evidence of tumor relapse.

Statistical analysis. Categorical variables were assessed using the chi-square test or Fisher exact test, and continuous variables were assessed using the *t*-test. Continuous variables were divided into two groups according to the median value (age, ICGR15, and tumor size) and normal cut off value (CA19-9). Patient OS and RFS were calculated using the Kaplan–Meier method, and comparison of survival curves was made with the log-rank test. Potential predictors of OS and RFS were evaluated in a multivariate Cox's proportional hazard model. *p*-Values less than 0.05 ($p<0.05$) were considered to indicate statistical significance. JMP software (version 13.0; SAS Institute, Cary, NC, USA) was used for statistical analysis.

Table I. *The patient characteristics*.

		Total
	Number	224
Gender	Male	154 (69%)
Age	Median, year	68 (26-91)
ICGR15	Median, %	10 (1-56)
	>10%,	97 (45%)
	≤10%	121 (55%)
Virus	Hepatitis C virus (HCV)	41 (18%)
	Hepatitis C virus (HBV)	15 (7%)
	Alcohol	16 (7%)
	NASH	20 (9%)
	Other	132 (58%)
No cancerous liver	Liver cirrhosis	24 (11%)
	Chronic hepatitis	95 (42%)
	Normal	105 (46%)
CA19-9	Median, mAU/l	61 (1-114,720)
	>61	103 (50%)
	≤61	102 (50%)
Surgical procedure	Tri-sectionectomy	11 (5%)
	Hemi hepatectomy	151 (67%)
	Sectionectomy	39 (17%)
	Segmentectomy	16 (7%)
	Partial resection	7 (3%)
Lymph node dissection	Absent	84 (37%)
	Present	140 (63%)
Size	Median, cm	4.5 (1-19)
	>4.5 cm	97 (43%)
	≤4.5 cm	127 (57%)
Macroscopic tumor type	Mass-forming (MF)	137 (61%)
	Periductal infiltrating (PI)	18 (8%)
	MF plus PI	69 (31%)
Portal vein invasion	Absent	47 (21%)
	Present	177 (79%)
Bile duct invasion	Absent	144 (64%)
	Present	80 (36%)
Intrahepatic metastasis	Absent	177 (79%)
	Present	47 (21%)
Lymph node metastasis	Absent	149 (67%)
	Present	75 (33%)
Adjuvant therapy	Chemotherapy	62 (28%)
	Immunotherapy	65 (29%)
	Absent	97 (43%)

ICGR15: Indocyanine green retention rate at 15 min; NASH: non-alcoholic steatohepatitis; PBC: primary biliary cholangitis.

Results

The patient clinical characteristics are shown in Table I. The mean patient follow-up was 47 months (ranging from 0.8 to 222 months). CA19-9, intrahepatic metastasis (IM), portal vein invasion (PVI), LNM, adjuvant chemotherapy, and adjuvant immunotherapy were significant prognostic factors for OS and RFS on univariate analysis (Table II). IM (relative risk 0.488, $p=0.002$), LNM (relative risk 0.401, $p<0.0001$), adjuvant chemotherapy (relative risk 0.307, $p<0.0001$), and adjuvant immunotherapy (relative risk 0.526, $p=0.0086$) were significant prognostic factors for OS on multivariate analysis (Table III). Similarly, IM (relative risk 0.343, $p<0.0001$), LNM (relative risk 0.603, $p=0.0064$), and adjuvant chemotherapy (relative risk 0.489, $p=0.0019$) were significant prognostic factors for RFS on multivariate analysis (Table III).

Therefore, surgical outcomes were compared considering subgroups based on the presence or absence of IM and LNM (Figure 1). The 5-year OS rates were 64% in 127 patients with

Table II. *Univariate analysis of overall survival rate and recurrence-free survival rate.*

	5-year OS rate	*p*-Value	5-year RFS rate	*p*-Value
ICGR15 (%),≤10 (n=121)/>10 (n=97)	43%/44%	0.93	31%/27%	0.69
Chronic liver disease, absent (n=127)/present (n=97)	39%/53%	0.16	32%/32%	0.91
CA19-9 (mAU/l), ≤61 (n=102)/>61 (n=103)	58%/29%	<0.0001	40%/22%	<0.0001
Surgical procedures, Hemihepatectomy (n=163)/Sectionectomy, or smaller (n=61)	41%/54%	0.18	33%/27%	0.52
Lymph node dissection, absent (n=84)/present (n=140)	54%/40%	0.1	29%/32%	0.75
Size (cm), ≤4.5 (n=127)/>4.5 (n=97)	48%/39%	0.2	30%/33%	0.41
Macroscopic tumor type, MF (n=137)/PI or MF+PI (n=87)	51%/35%	0.08	33%/28%	0.84
Portal vein invasion, absent (n=47)/present (n=177)	72%/36%	0.0006	50%/26%	0.0006
Intrahepatic metastasis, absent (n=177)/present (n=47)	53%/16%	<0.0001	40%/0%	<0.0001
Lymph node metastasis, absent (n=149)/present (n=75)	55%/25%	<0.0001	39%/17%	<0.0001
Adjuvant chemotherapy (n=62)/Adjuvant immunotherapy (n=65)/absent (n=97)	57%/50%/32%	0.0006	39%/35%/22%	0.0098

OS: Overall survival; RFS: recurrence-free survival; ICGR15: indocyanine green retention rate at 15 min; MF: mass-forming; PI: periductal infiltrating.

Table III. *Multivariate analysis of overall survival rate and recurrence-free survival rate.*

Survival	Relative risk	95%CI	*p*-Value
Portal vein invasion, absent/present	0.431	[0.431, 0.796]	0.0062
Intrahepatic metastasis, absent/present	0.522	[0.329, 0.839]	0.0078
Lymph node metastasis, absent/present	0.447	[0.289, 0.691]	0.0003
Adjuvant chemotherapy, present/absent	0.324	[0.173, 0.576]	<0.0001
Adjuvant immunotherapy, present/absent	0.478	[0.288, 0.781]	0.0031
Recurrence	**Relative risk**	**95%CI**	***p*-Value**
CA19-9 (mAU/l), ≤61/>61	0.665	[0.453, 0.972]	0.0349
Intrahepatic metastasis, absent/present	0.341	[0.228, 0.513]	<0.0001
Lymph node metastasis, absent/present	0.616	[0.428, 0.889]	0.0098
Adjuvant chemotherapy, present/absent	0.519	[0.323, 0.814]	0.0041
Adjuvant immunotherapy, present/absent	0.738	[0.481, 1.120]	0.15

neither IM nor LNM, 32% in 50 patients with LNM and no IM, 35% in 22 patients with IM and no LNM, and 5% in 25 patients with both IM and LNM (Figure 1A). The 5-year OS rate was significantly higher in patients with neither IM nor LNM than in patients with LNM and no IM (p=0.0006), in patients with IM and no LNM (p=0.0006), and in patients with both IM and LNM (p<0.0001). The 5-year RFS rates were 45% in 127 patients with neither IM nor LNM, 28% in 50 patients with LNM and no IM, 12% in 22 patients with IM and no LNM, and 0% in 25 patients with both IM and LNM (Figure 1B). The 5-year RFS rate was significantly higher in patients with neither IM nor LNM than in patients with LNM and no IM (p=0.0268), in patients with IM and no LNM (p=0.0200), and in patients with both IM and LNM (p=0.0123).

Outcomes were compared considering subgroups based on the adjuvant therapy. In 127 patients with neither IM nor LNM, the 5-year OS and RFS rates were significantly higher in 36 patients with chemotherapy (81% and 57%) and in 34 patients with immunotherapy (68% and 50%) than in 57 patients with hepatectomy alone (45% and 33%, Figure 2A and Figure 3A). In 50 patients with LNM and no IM, the 5-year OS rate was significantly higher in 14 patients with chemotherapy (42%) and 20 patients with immunotherapy (47%) than in 16 patients with hepatectomy alone (8%, Figure 2B). However, there were no significant differences in RFS rates among patient groups (Figure 3B). In 22 patients with IM and no LNM, there were no significant differences in OS and RFS rates among patient groups (Figure 2C and Figure 3C). In 25 patients with both IM and LNM, there were no significant differences in OS and RFS rates among patient groups (Figure 2D and Figure 3D).

Discussion

ICC is a fatal disease because of frequent recurrence and mortality despite curative surgery. The rate of intrahepatic

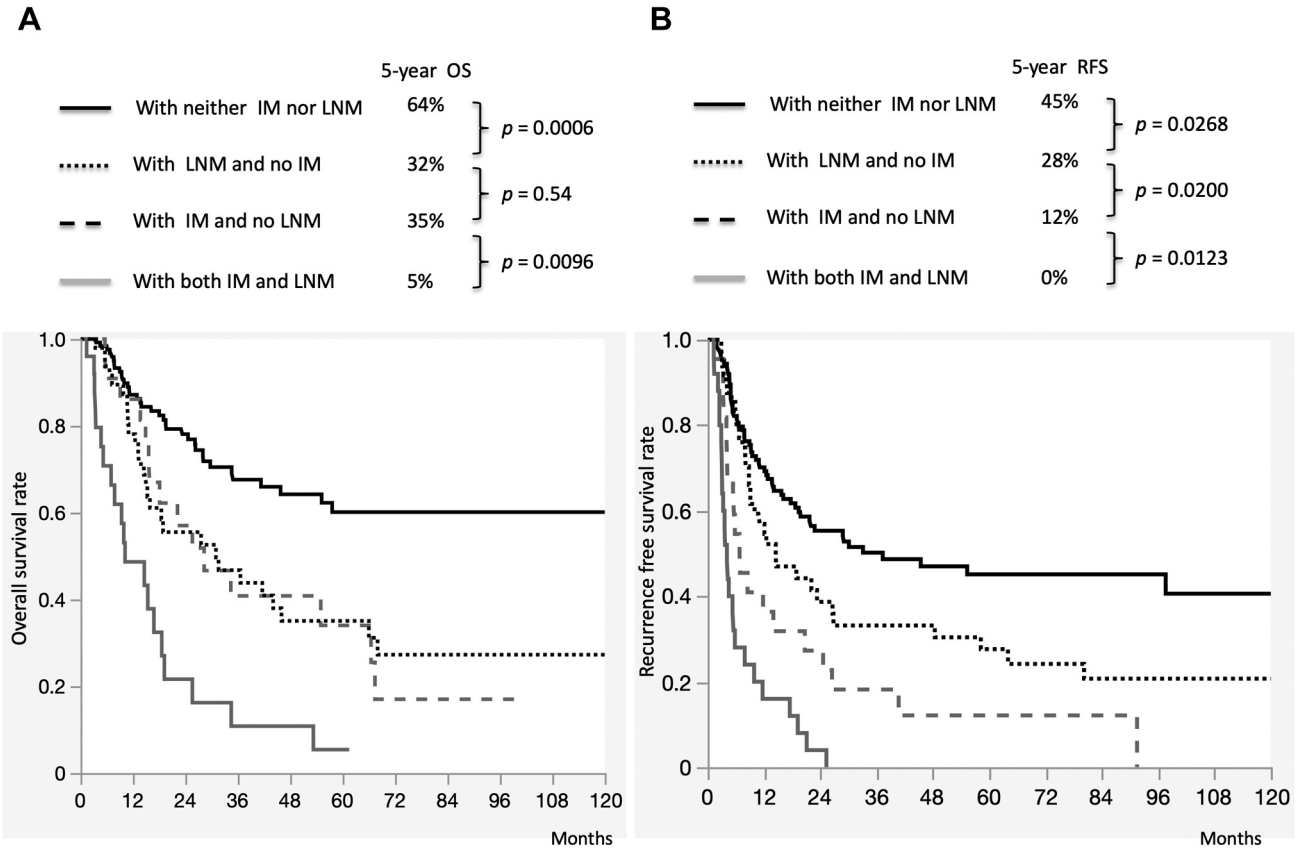

Figure 1. *Overall survival (A) and recurrence-free survival curves (B) in relation to intrahepatic metastasis and lymph node metastasis.*

recurrence after curative surgery for the MF type of ICC is particularly high, with a 5-year survival rate of approximately 20-40% (4-12). The survival rates of patients with ICC have improved recently (10, 12). The indications of hepatectomy for ICC were therefore reevaluated. In our present study, IM and LNM were found to be prognostic factors for OS and RFS by multivariate analyses. In patients with ICC, the absence of IM or LMN was found to be the optimal indication for hepatectomy because the 5-year OS rate was 64% and the 5-year RFS rate was 45%. However, the presence of both IM and LNM, was not found to be an indication for hepatectomy because the 5-year OS rate was only 5% despite curative hepatectomy.

Previously, tumor number and LNM have been shown to be prognostic factors of ICC (5-12). The survival rates of patients with solitary ICC have improved recently. Uchiyama *et al*. investigated prognostic factors in 314 patients with ICC in 2011, and reported that multiple tumors was significant prognostic factor of ICC and the 5-year OS rate was 36% in patients with solitary ICC (5). Sakamoto *et al*. investigated 419 patients with ICC in 2016, and reported that multiple tumors was significant prognostic factor on multivariate analysis and the 5-year OS rate was 54% in patients with solitary ICC (10). According to the 19th Report of the LCSGJ (2006-2007), 5-year OS rate was 44% in patients with solitary ICC (11). Recently, 5-year OS rate was up to 56% in patients with solitary ICC according to the 22nd Report of LCSGJ (2012-2013) (12).

The survival rates of patients without LNM have improved recently. Uchiyama *et al*. reported that LNM was significant prognostic factor of ICC and the 5-year OS rate was 46% in patients without LNM (5). Sakamoto *et al*. reported that LNM was significant prognostic factor on multivariate analysis and the 5-year OS rate was 58% in patients without LNM (10). According to the 19th Report of the LCSGJ, the 5-year OS rate was 47% in patients without LNM. In the recent 22nd Report of LCSGJ, the 5-year OS rate of patients with LNM was up to 56% (12). In our present study, in patients with neither IM nor LNM, the 5-year OS rate was 64% and the 5-year RFS rate was 45%. Therefore, the absence of IM or LNM is the optimal indication for hepatectomy in patients with ICC.

Efficacy of chemotherapy with gemcitabine and cisplatin for unresectable ICC has been reported (19). Recently,

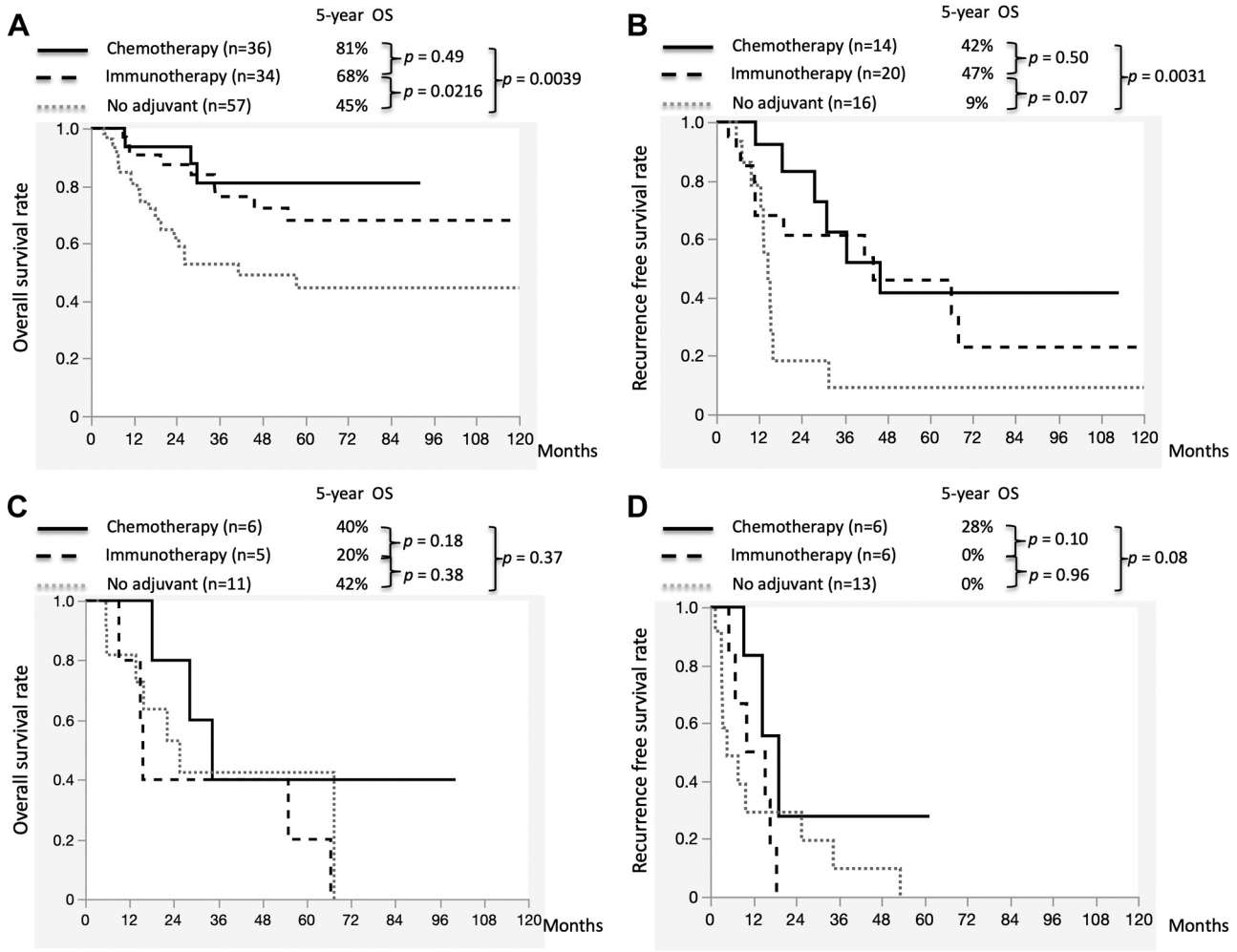

Figure 2. *Survival curves in relation to the adjuvant therapy in patients with neither intrahepatic metastasis (IM) nor lymph node metastasis (LNM) (A), in patients with LNM and no IM (B), in patients with IM and no LNM (C), and in patients with both IM and LNM (D).*

adjuvant therapy with capecitabine or S-1 after surgery in patients with biliary tract cancer has been reported (13, 14). Primrose *et al*. investigated OS rates in 447 patients with biliary tract cancer (including 84 patients with ICC) and reported better OS rates in 210 patients with adjuvant therapy with capecitabine (13). However, the report gave no details or subgroup analysis on the patients with ICC, such as presence or absence of IM or LNM. In our present study, adjuvant chemotherapy and adjuvant immunotherapy were significant prognostic factors for OS and RFS on multivariate analysis. Especially, the absence of IM or LNM was found to be the optimal indication for hepatectomy with adjuvant therapy because the 5-year OS and RFS rates were significantly higher in 36 patients with chemotherapy and in 34 patients with immunotherapy compared to those in 57 patients with hepatectomy alone. Therefore, the absence of IM or LNM was the optimal indication for adjuvant therapy after surgery.

Previous reports showed that the survival rates in patients with LNM despite curative surgery were 10% or less, at 5 years (5, 7, 9). In our present study, significantly better OS rate was observed in 14 patients with adjuvant chemotherapy and 20 patients with adjuvant immunotherapy among 50 patients with LNM and no IM. Ten of 50 patients with LNM and no IM survived 5 years or more, 3 patients underwent adjuvant chemotherapy, 6 patients underwent adjuvant immunotherapy, and 1 patient underwent hepatectomy alone. Therefore, LNM and no IM is good indication for adjuvant chemotherapy and immunotherapy after surgery of patients with ICC. However, there was no significant difference in OS and RFS rates according to adjuvant therapy in 25 patients with both IM and LNM. In 25 patients with both IM and LNM, no patient survived 5 years or more after hepatectomy. Therefore, the presence of both IM and LNM is not an indication for surgery in patients with ICC.

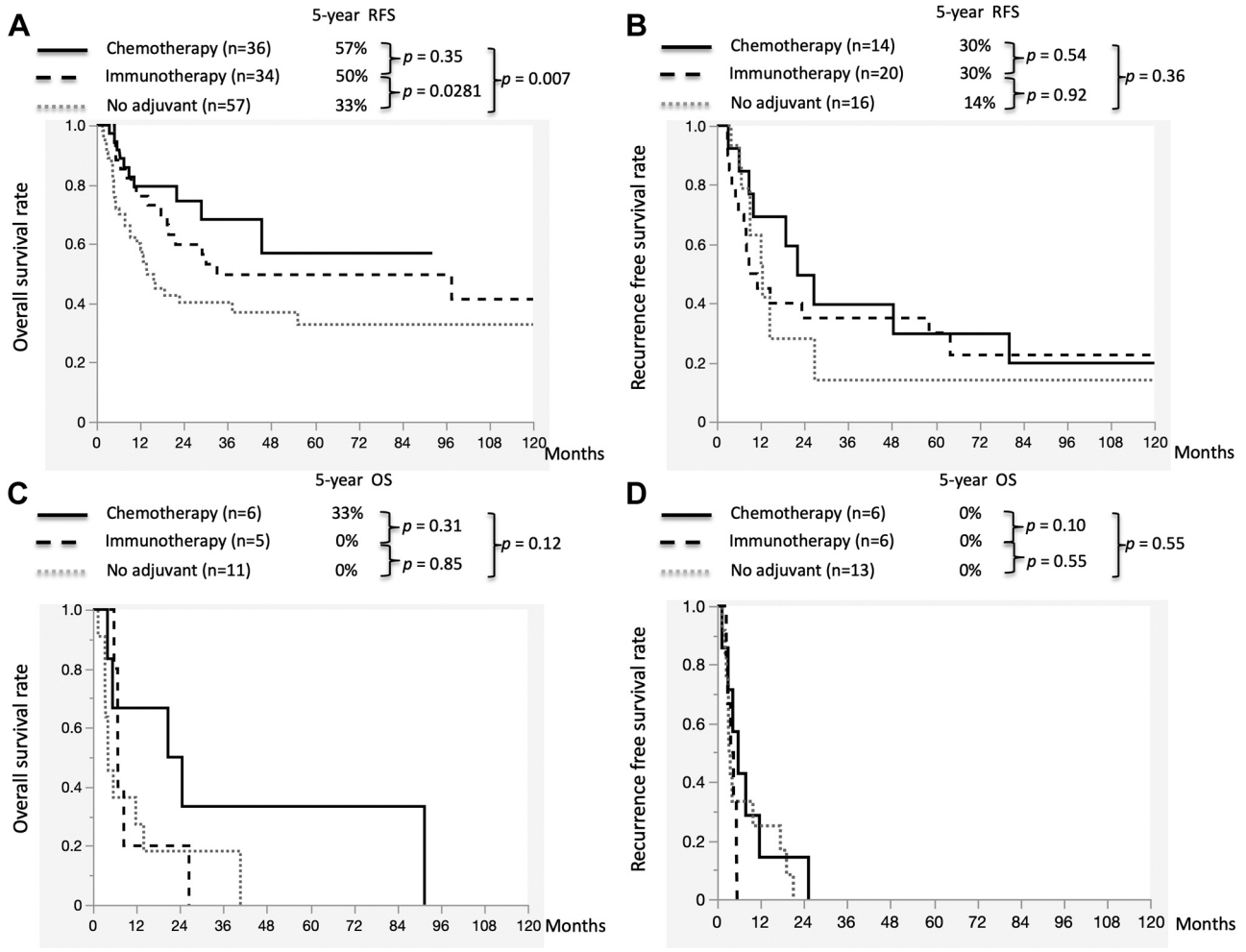

Figure 3. *Recurrence-free survival curves in relation to the adjuvant therapy in patients with neither intrahepatic metastasis (IM) nor lymph node metastasis (LNM) (A), in patients with LNM and no IM (B), in patients with IM and no LNM (C), and in patients with both IM and LNM (D).*

Conclusion

The indication of surgery in patients with ICC can be determined based on the presence or absence of IM and LNM. The absence of IM or LNM is the optimal indication for hepatectomy and adjuvant therapy after surgery.

Conflicts of Interest

The Authors have no conflicts of interest to disclose in relation to this study.

Authors' Contributions

Conception and design, acquisition of data, and analysis and interpretation of data, drafting the article, and final approval of the manuscript: Shunichi Ariizumi and Masakazu Yamamoto. Acquisition of data and interpretation of data; critical revision for important intellectual content; final approval of the manuscript: Yoshihito Kotera, Ryota Higuchi, Shingo Yamashita, Takaaki Kato, Yoshihiro Hirata, Goro Honda, Satoshi Katagiri, Hiroto Egawa.

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