Surgery 166 (2019) 975–982

Contents lists available at ScienceDirect

Surgery

journal homepage: www.elsevier.com/locate/surg

Bile duct/Gallbladder

Prognostic value of lymphadenectomy for long-term outcomes in node-negative intrahepatic cholangiocarcinoma: A multicenter study

Tomoaki Yoh, MD, PhD[a,b], François Cauchy, MD[a], Bertrand Le Roy, MD, PhD[a], Satoru Seo, MD, PhD[b], Kojiro Taura, MD, PhD[b], Christian Hobeika, MD[a], Safi Dokmak, MD, PhD[a], Oliver Farges, MD, PhD[a], Maximiliano Gelli, MD[a], Antonio Sa Cunha, MD, PhD[c], René Adam, MD, PhD[c], Shinji Uemoto, MD, PhD[b], Olivier Soubrane, MD[a,*]

[a] *Department of Hepatobiliopancreatic Surgery and Liver Transplantation, Beaujon Hospital, Clichy, Assistance Publique, Hôpitaux de Paris, Université Paris VII Denis Diderot, Paris, France*
[b] *Department of Surgery, Graduate School of Medicine, Kyoto University, Kyoto, Japan*
[c] *Department of Surgery, Assistance Publique, Hôpitaux de Paris, Hôpital Paul-Brousse, Centre Hépato-Biliaire, Université Paris-Sud, Institut National de la Santé et de la Recherche Médicale U935, Villejuif, France*

ARTICLE INFO

Article history:
Accepted 21 June 2019
Available online 14 August 2019

ABSTRACT

Background: Lymphadenectomy ensures accurate staging for patients with intrahepatic cholangiocarcinoma, especially for those without preoperatively suspected positive lymph nodes (clinically node-negative); however, its prognostic value has been poorly documented. The aim of this study was to evaluate the prognostic value of lymphadenectomy on long-term outcomes in patients undergoing surgery for clinically node-negative intrahepatic cholangiocarcinoma.
Methods: Data from all patients who underwent liver resection with or without lymphadenectomy for preoperatively diagnosed intrahepatic cholangiocarcinoma between 2000 and 2016 at 3 tertiary hepatobiliary centers were analyzed retrospectively. Propensity score matching in a 1:1 ratio was conducted based on clinically relevant covariates between patients with clinically node-negative intrahepatic cholangiocarcinoma who underwent liver resection with (LND group) and without (NLND group) lymphadenectomy. Overall survival and disease-free survival were compared in the matched cohort.
Results: Among 350 patients who underwent surgery during the study period, 192 (55%) with clinically node-negative intrahepatic cholangiocarcinoma met the inclusion criteria. After propensity score matching, 2 well-balanced groups of 56 patients each were analyzed. There was no significant difference regarding postoperative variables among these 112 matched patients. Patients who underwent a liver resection with lymphadenectomy achieved better 3- and 5-year overall survival (78% and 65% vs 52% and 46%, $P = .017$) and disease-free survival (46% and 34% vs 31% and 31%; $P = .042$) compared with patients who underwent liver resection without lymphadenectomy.
Conclusion: Lymphadenectomy can be associated with better long-term outcomes in patients with node-negative intrahepatic cholangiocarcinoma. Our data may support routine lymphadenectomy for node-negative intrahepatic cholangiocarcinoma with the objective of achieving better long-term outcomes.

Introduction

Lymph node (LN) metastasis is one of the most prominent prognostic factors associated with poor prognosis in patients undergoing operation for intrahepatic cholangiocarcinoma (ICC).[1–5] Preoperative imaging is not reliable enough for the screening of LN metastasis.[6,7] Therefore, routine lymphadenectomy of the perihepatic area with the objective of ensuring staging remains advocated by the majority of hepatobiliary surgeons.[3–5]

Nonetheless, recent studies of national databases have highlighted the fact that many surgeons, especially those in Western countries, only perform selective lymphadenectomy,[8–10] reflecting the concept that many surgeons are still skeptical about the relevance of routine lymphadenectomy in patients with ICC. Indeed, one reason is the lack of evidence as to the prolonged survival effect

* Reprint requests: Olivier Soubrane, MD, Department of Hepatobiliopancreatic Surgery and Liver Transplantation, Beaujon Hospital, Clichy, Assistance Publique, Hôpitaux de Paris, Université Paris VII Denis Diderot, Paris, France.
E-mail address: olivier.soubrane@aphp.fr (O. Soubrane).

https://doi.org/10.1016/j.surg.2019.06.025
0039-6060/

of lymphadenectomy.[1] Another reason is that curative resection for ICC often requires major liver resection[11,12] and that additional extensive lymphadenectomy may lead to devascularization of the common bile duct or chylous ascites and thus increase the risk of postoperative complications.[13,14] Ideally, an optimal balance between minimal operative risk and maximal oncologic benefit should be obtained. Unfortunately, this concern has led to substantial heterogeneity regarding the practices of lymphadenectomy for ICC, which further complicates the interpretation of its oncologic role.

Currently, lymphadenectomy for preoperatively suspected regional-positive LNs (clinically node-positive) in patients with ICC has gained a consensus, as suggested by the guidelines of the European Association for the Study of the Liver[1]; yet, the clinical relevance of lymphadenectomy in patients without preoperatively suspected positive LNs (clinically node-negative) remains poorly documented. To the best of our knowledge, no multicenter study exploring the prognostic role of lymphadenectomy on long-term outcomes in clinically node-negative ICC has been conducted to date. The present study, therefore, aimed to compare the long-term outcomes of patients with clinically node-negative ICC who underwent liver resection with and without lymphadenectomy.

Methods

Study design

This study aimed to assess the clinical importance of lymphadenectomy on long-term outcomes in clinically node-negative ICC using patients from 3 tertiary hepatobiliary centers (Beaujon Hospital, Paris, France; Paul Brousse Hospital, Villejuif, France; and Kyoto University Hospital, Kyoto, Japan) involving different treatment strategies and rates of lymphadenectomy. Patients were divided into 2 groups: those who underwent lymphadenectomy (LND group) and those who did not (NLND group). Overall survival (OS) and disease-free survival (DFS) between the 2 groups were compared. Survival after recurrence was also compared in patients who had a recurrence during the follow-up period. To directly compare the prognostic value of lymphadenectomy between the 2 groups, a propensity score–matching study was performed.

In the Japanese cohort, the protocol of this study was approved by the ethical committee of the Graduate School of Medicine, Kyoto University (approval code: R1568). In the French cohort, given the purely observational and retrospective nature of the study, informed written consent and institutional review board approval was waived according to the French legislation. This study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology statement.[15]

Patient selection criteria

We extracted data from the respective institutional databases for all consecutive patients with ICC with a clear mass component[16] who underwent liver resection with or without lymphadenectomy at the 3 hospitals between January 2000 and December 2016. The inclusion criteria were (1) preoperatively diagnosed ICC and (2) no apparent distant metastases, including distant or para-aortic LNs. The diagnosis of ICC was based on radiologic or biologic criteria associated with percutaneous biopsy in doubtful cases. Diagnosis of ICC was retained only if the biliary origin of the tumor was confirmed explicitly by the tumor that arose from the parenchyma or second or higher-order branches of the intrahepatic bile ducts.[16,17] This study included patients with combined hepatocellular carcinoma-cholangiocarcinoma who were diagnosed preoperatively as having ICC. Patients who underwent any preoperative therapy (ie, preoperative chemotherapy, radiotherapy, or previous liver resection with lymphadenectomy) were excluded because of the difficulty in evaluating clinical nodal status. Postoperative deaths (within 90 postoperative days) were excluded from survival analyses.

Definition of node-negative ICC

Computed tomography was conducted routinely for the preoperative assessment across the 3 hospitals; therefore, the clinical LN status was defined on the basis of computed tomography findings in this study. Node-negative ICC was defined as disease without any suspicious or positive regional LNs, as determined by institutional radiologists. Criteria for suspicious or positive LNs on computed tomography were based on the following general criteria[18,19]: size of the LNs (short-axis diameter >10 mm), contrast enhancement, abnormal shape, and the presence of central necrosis or extra-nodal extension. Preoperative regional LN evaluation was based on the following areas: hilar (common bile duct, hepatic artery, portal vein, and cystic duct), periduodenal, peripancreatic, and gastrohepatic LNs.[17,20]

Data collection and follow-up

Clinical and pathologic stages were determined based on the reports confirmed by at least 2 dedicated hepatobiliary radiologists and pathologists. Tumor classifications were assessed in accordance with the eighth American Joint Committee on Cancer staging system.[21] In this study, T2–T4 tumors were defined as advanced T stage because multiple tumors have been shown to impair survival (ie, presence of multiple tumors is automatically categorized as the T2 stage or a more advanced stage).[22,23] In contrast, a T1 tumor, which represents a solitary tumor with no vascular invasion, was defined as an early-stage tumor. LN metastasis was defined as the presence of metastatic LNs in the regional area. The 2000 Brisbane classification of the International Hepato-Pancreato-Biliary Association was used to describe the extent of the liver resection (ie, major resection when ≥3 contiguous segments, minor resection when <3 segments).[24] Operative morbidity was evaluated according to the Dindo-Clavien classification.[25] The histologic liver background was assessed using the METAVIR score.[26] In this setting, cirrhosis accounted for F4 fibrosis, and severe fibrosis accounted for F3 and F4 fibroses. Follow-up data were obtained by contacting referring physicians or the tumor registry. Follow-up data were updated in February 2018.

Operative procedures and treatment strategy

Therapeutic options and operative strategies were discussed in a weekly multidisciplinary tumor meeting, which included at least 2 medical oncologists, dedicated hepatobiliary radiologists, and senior hepatobiliary surgeons from all 3 hospitals. Resectability was considered based on the following: clinical conditions; hepatic functional reserve; volume of future liver remnant; vascular and nodal involvement; and the size, number, and location of the tumor. In the 2 French centers, whether selective lymphadenectomy around the hepatoduodenal ligament was extended to other selected areas was decided by senior surgeons on a case-by-case basis. In Kyoto University Hospital, routine lymphadenectomy around the hepatoduodenal ligament, retropancreatic area, and the common hepatic artery was performed with consideration of the patient's age and hepatic functional reserve; in left-sided tumors, usually only a sampling of LNs around the lesser curvature of the stomach was performed to avoid delayed gastric emptying. Biliary resection and reconstruction were considered when tumors

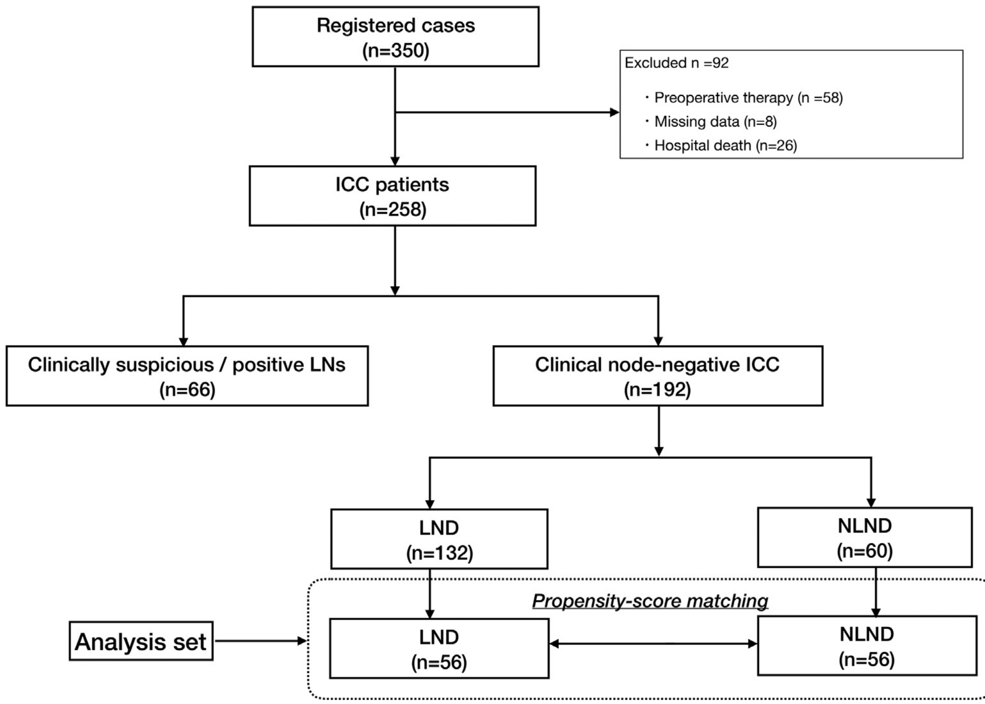

Fig 1. Flow chart showing patient disposition.

involved the hepatic hilum. Vascular resection or reconstruction were considered, if necessary. The indications for postoperative adjuvant therapy were determined during the multidisciplinary team meeting in each hospital.

Statistical analysis

A propensity score was calculated using a logistic regression model, including preoperative variables considered to be directly associated with selection of lymphadenectomy. All statistically significant pre- and perioperative variables were included to establish the model. These variables included age, sex, underlying liver disease, tumor location, clinical T stages, extent of liver resection, biliary reconstruction (ie, alternative to the ICC with hilum invasion), and vascular resection. After generation of the propensity score, patients in the LND and NLND groups underwent 1:1 nearest-available matching of the logit of the propensity score with a caliper width of 0.20 of the standard deviation of the score.[27] Patients in both the LND and NLND groups who did not meet the matching criteria were excluded. As the magnitude of statistical significance is strongly influenced by the sample size, the balance of each covariate before and after the matching between the 2 groups was also evaluated by standardized differences. A standardized mean difference of <.100 indicates very small differences, values between .100 and .300 indicate small differences, values between .300 and .500 indicate moderate differences, and values >.500 indicate considerable differences.[28]

All statistical analyses for outcomes were performed on all matched-paired patients. Categorical variables were analyzed with the Fisher exact test. OS was calculated from the date of operation until death owing to any cause or the date of the last follow-up. DFS was calculated from the date of the operation until the date of confirmed recurrence, or any cause of death. Survival after resection was calculated from the date of the recurrence until the date of any cause of death. Survival curves were estimated using the Kaplan-Meier method compared with the generalized Wilcoxon test. All *P* values were 2 sided. All statistical computations were performed using JMP Pro12.1 software (SAS Institute, Inc, Cary, NC). Propensity score matching was performed using the JMP add-in program.

Results

A total of 350 patients with ICC underwent curative-intent resection during the study period (Beaujon Hospital, $n = 113$; Paul Brousse Hospital, $n = 108$; Kyoto University Hospital, $n = 129$). Based on the study criteria, 92 patients were excluded because of preoperative therapy ($n = 58$), missing data ($n = 8$), and postoperative death ($n = 26$). Of the remaining 258 patients, 192 (55%) with clinical node-negative ICC were considered in this study (Fig 1). There was no difference in OS and DFS between the French and Japanese cohorts, according to the presence and absence of lymphadenectomy (Fig 2).

Patient clinical characteristics

Of the 192 patients with node-negative ICC, 132 underwent lymphadenectomy and 60 did not. Using the propensity score, 112 patients with ICC were matched into either the LND group or the NLND group, composed of 56 patients each (Fig 1). Table I summarizes the clinical data of the overall cohort and matched cases. Before matching, the proportion of major liver resection and biliary reconstruction was greater in the LND group compared with the NLND group ($P = .023$ and $P = .019$). After propensity score matching, there was no difference between the 2 groups, and the standardized differences were <.100 in the 8 selected variables for the model of propensity score matching. The LND group included a greater proportion of the Japanese cohort than the NLNS group ($P < .001$).

Postoperative characteristics

The postoperative findings are summarized in Table II. Before matching, the incidence of LN metastasis confirmed by

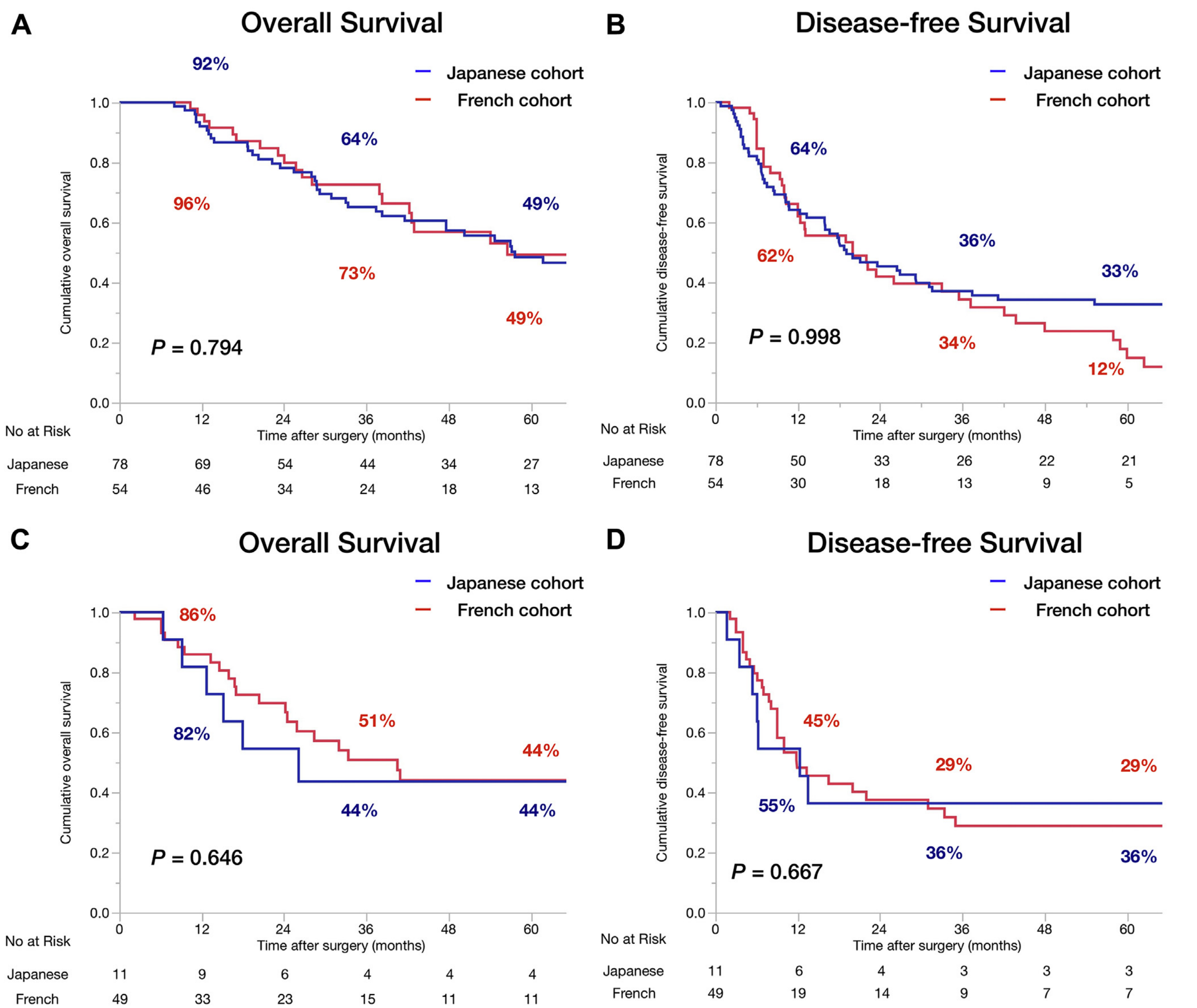

Fig 2. Overall survival (OS) (*A*) and disease-free survival (DFS) (*B*) of patients with intrahepatic cholangiocarcinoma (ICC) who underwent liver resection with lymphadenectomy between the Japanese and French cohorts. OS (*C*) and DFS (*D*) of patients with ICC who underwent liver resection without lymphadenectomy between Japanese and French cohorts.

lymphadenectomy was 17% (22 of 132 patients). On final pathologic examination, 6 (3%) patients were reclassified as having combined hepatocellular carcinoma-cholangiocarcinoma. In the matched cohort, the occurrence of overall postoperative major complications (Dindo-Clavien classification IIIa-IV) was comparable between the 2 groups ($P = 1.000$). On pathologic examination, there were no differences with regard to distributions of the pathologic T stage ($P = 1.000$), resection margin status ($P = .629$), tumor size ($P = .99$), tumor number ($P = .433$), microvascular involvement ($P = .702$), tumor differentiation ($P = .788$), and liver parenchymal background ($P = .776$) between the 2 groups. Incidence of LN metastasis confirmed by lymphadenectomy decreased to 9% (5 of 56 patients) after matching. There was no difference in performance of postoperative adjuvant therapy between the 2 groups ($P = .181$).

Long-term outcomes

Median follow-up was 28.4 months. Median OS was 73.2 months, with 1-, 3-, and 5-year OS rates of 89%, 66%, and 56%, respectively. Median DFS was 19.1 months, and corresponding 1-, 3-, and 5-year DFS rates were 60%, 39%, and 32%, respectively.

Patients in the LND group had better OS and DFS compared with those in the NLND group (Fig 3). In the LND group, the median OS rate was 94.2 months and 1-, 3-, and 5-year OS rates were and 94%, 78%, and 65%, respectively. In the NLND group, the median OS rate was 40.5 months and 1-, 3-, and 5-year OS rates were 84%, 52%, and 46%, respectively ($P = .017$). Regarding DFS, for the LND group, the median DFS was 26 months and 1-, 3-, and 5-year DFS rates were 68%, 46%, and 34%, respectively. In the NLND group, median DFS was 12.3 months and 1-, 3-, and 5-year DFS rates were 52%, 31%, and 31%, respectively ($P = .042$).

Recurrence

Finally, we analyzed the association between the patterns of recurrence and the presence or absence of lymphadenectomy. During the follow-up, tumor recurrences were identified in 61 (55%) patients: 30 (49%) patients in the LND group and 31 (51%)

Table I
Clinical patients and tumor characteristics in patients with node-negative ICC before and after matching

	Before matching (n = 192)				After matching (n = 112)			
	LND Group (n = 132)	NLND Group (n = 60)	P value	Standardized difference	LND Group (n = 56)	NLND Group (n = 56)	P value	Standardized difference
Age (y) (median [range])	66 (26–84)	68 (27–83)	.272	.148	67.5 (34–83)	68 (27–87)	.664	.037
Sex (male)	68 (52)	33 (55)	.755	.070	33 (56)	30 (56)	.703	—
Underlying liver disease	27 (21)	16 (27)	.355	.149	13 (23)	15 (27)	.828	.083
Virus hepatitis	18 (14)	11 (18)						
Others	9 (7)	5 (8)						
No	105 (80)	44 (73)			43 (77)	41 (73)		
AJCC clinical T status			.256	.187			.837	.076
T1	25 (19)	16 (27)			18 (32)	16 (29)		
T2–T4	107 (81)	44 (73)			38 (68)	40 (71)		
Left-sided tumor	67 (51)	27 (45)	.534	.116	26 (46)	27 (48)	1.000	.036
Major liver resection	103 (78)	37 (62)	.023*	.361	35 (63)	37 (66)	.844	.075
Biliary reconstruction	27 (21)	4 (7)	.019*	.411	4 (7)	4 (7)	1.000	—
Vascular resection	20 (15)	4 (7)	.156	.275	4 (7)	4 (7)	1.000	—
Institution†								
Japan	78 (59)	11 (18)	<.001	.922	34 (61)	10 (18)	<.001	.975
France	54 (41)	49 (82)			22 (39)	46 (82)		

Data are n (%), unless otherwise indicated. A standardized mean difference of <.100 indicates very small differences, values between .100 and .300 indicate small differences, values between .300 and .500 indicate moderate differences, and values >.500 indicate considerable differences.
Fisher exact test is used for categorical analyses.
Tumor stage is classified by the 8th AJCC staging system.
AJCC, American Joint Committee on Cancer.
* $P < .05$ is a significant difference.
† Distribution of institution was excluded from creating the propensity score–matched model.

Table II
Operative outcomes and postoperative variables in patients with node-negative ICC before and after matching

	Before Matching (n = 192)			After Matching (n = 112)		
	LND Group (n = 132)	NLND Group (n = 60)	P value*	LND Group (n = 56)	NLND Group (n = 56)	P value*
Morbidity						
None or I/II	100 (76)	45 (75)	1.000	43 (77)	42 (75)	1.000
III/VI	32 (24)	15 (25)		13 (23)	14 (25)	
Pathologic T classification						
T1	47 (36)	24 (40)	.629	23 (41)	24 (43)	1.000
T2–T4	85 (64)	36 (60)		33 (59)	32 (57)	
Pathologic LN metastasis						
Negative	110 (83)	—	—	51 (91)	—	—
Positive	22 (17)	—		5 (9)	—	
Differentiation						
Poorly	20 (15)	8 (13)	.828	9 (16)	7 (13)	.788
Well/moderate	112 (85)	52 (87)		51 (84)	49 (88)	
Tumor diameter						
>5 cm	64 (49)	34 (57)	.351	29 (52)	30 (54)	1.000
≤5 cm	68 (52)	26 (43)		27 (48)	26 (46)	
Tumor number						
Solitary	88 (67)	35 (58)	.330	38 (68)	33 (59)	.433
Multiple	44 (33)	25 (42)		18 (32)	23 (41)	
Microvascular invasion						
Yes	79 (60)	35 (58)	.875	34 (61)	31 (55)	.702
No	53 (40)	25 (42)		22 (39)	25 (45)	
Final diagnosis						
Cholangiocarcinoma	129 (98)	57 (95)	.379	53 (95)	53 (95)	1.000
cHCC-CC	3 (2)	3 (5)		3 (5)	3 (5)	
Resection margin						
Negative	108 (82)	46 (77)	.437	47 (84)	44 (79)	.629
Positive	24 (18)	14 (23)		9 (16)	12 (21)	
Liver fibrosis (F3/F4)	16 (12)	12 (20)	.186	8 (14)	11 (19)	.616
Adjuvant therapy						
Yes	62 (47)	23 (38)	.277	28 (50)	20 (36)	.181
Gemcitabine-based regimen	50 (38)	22 (37)		22 (39)	19 (34)	
5-FU–based regimen	9 (7)	1		6 (11)	1	
No	70 (53)	37 (62)		28 (50)	36 (64)	

Data are n (%), unless otherwise indicated.
Tumor classification is classified by 8th American Joint Committee on Cancer staging system.
cHCC-CC, combined hepatocellular carcinoma-cholangiocarcinoma.
* Fisher exact test is used for categorical analyses.

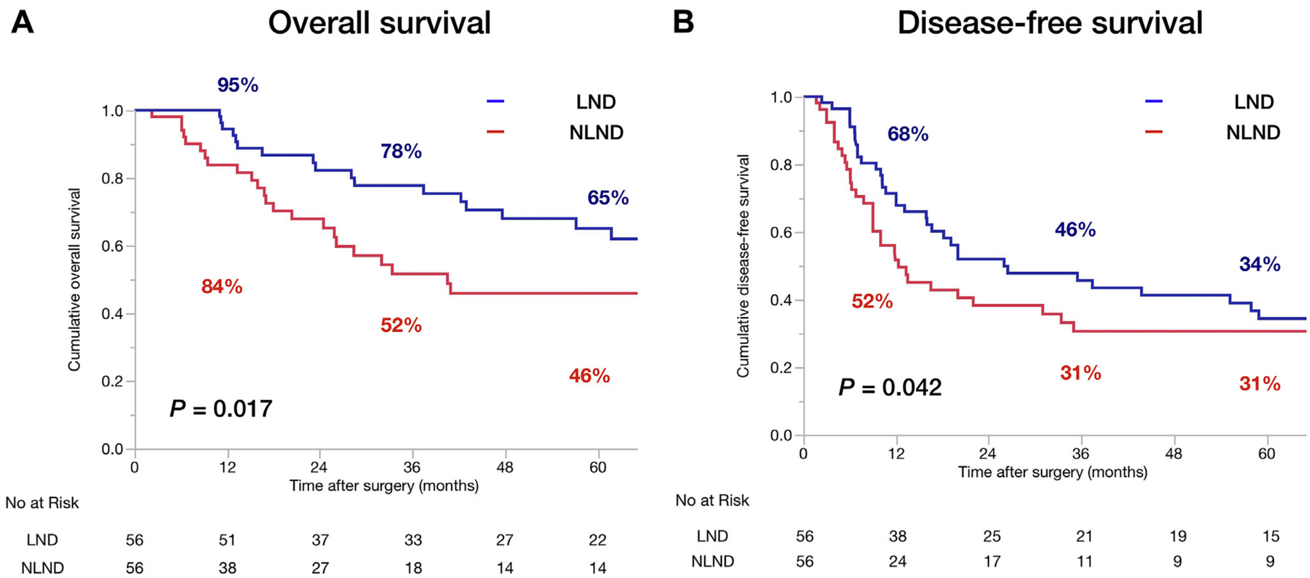

Fig 3. Overall survival (*A*) and disease-free survival (*B*) of the patients with intrahepatic cholangiocarcinoma in the matched cohort.

Table III
Association between recurrence and lymphadenectomy in patients with node-negative ICC

	LND Group (n = 30)	NLND Group (n = 31)	*P* value*
Pattern of recurrence			
Intrahepatic recurrence	8 (7)	11 (36)	.722
Extrahepatic recurrence	13 (43)	13 (42)	
Intra- plus extrahepatic recurrence	9 (30)	7 (23)	
Nodal recurrence	9 (30)	10 (33)	.849
Main treatment variables			.344
Systemic chemotherapy	21 (70)	19 (61)	
Operative treatment	7 (2)	5 (16)	
Palliative therapy	0	2 (7)	
Other	2 (7)	5 (16)	

Data are n (%), unless otherwise indicated.
* Fisher exact tests are used for categorical analyses.

patients in the NLND group. The patterns of recurrence were divided into 3 types: intrahepatic, extrahepatic, and intra- plus extrahepatic recurrence. Besides this, the nodal recurrence was analyzed. Table III shows the patterns of disease recurrence and the main treatments between the 2 groups. No difference was observed regarding patterns of disease recurrence and nodal recurrence between the 2 groups (P = .722 and P = .849). Systemic chemotherapy was the main treatment in recurrent patients between the 2 groups. No differences were observed in the treatment variables (P = .344). Median survival after recurrence was 17.2 months, with 1-, 3-, and 5-year rates of 65%, 26%, and 18%, respectively. Patients in the LND group tended to have better survival rates after recurrence compared with those in the NLND group (P = .074; Fig 4). In the LND group, median survival after recurrence was 23 months and 1-, 3-, and 5-year rates were 67%, 41%, and 23%, respectively. In the NLND group, median survival after recurrence was 14 months and 1-, 3-, and 5-year rates were 54%, 21%, and 17%, respectively.

Discussion

Although lymphadenectomy ensures accurate staging, its prognostic value for node- negative ICC has remained debated, resulting in heterogeneous operative practices in patients with ICC. This study evaluated the prognostic value of lymphadenectomy on long-term survival in patients with clinical node-negative ICC on preoperative imaging using a large, well-matched cohort of patients from 3 tertiary hepatobiliary centers (2 in France and 1 in Japan). In this setting, the results of the present study highlight that lymphadenectomy may be associated with a substantial survival benefit in patients with clinical node-negative ICC and further emphasizes the value of lymphadenectomy for patients with ICC.

Several studies have attempted to evaluate the prognostic impact of lymphadenectomy in patients undergoing liver resection for ICC,[29–32] but when interpreting the prognostic value of lymphadenectomy for ICC, several methodologic limitations and problems are observed. First, these studies were retrospective, single-center studies, which complicates obtaining a relevant control group to assess the value of lymphadenectomy. The best methods to evaluate the value of lymphadenectomy may be a multicenter analysis involving different treatment strategies and rates of lymphadenectomy. In this regard, our series provides better comparability between LND and NLND patients. Second, data focusing on patients in relevant clinical settings are often lacking. Although lymphadenectomy in clinically node-positive ICC patients has gained a consensus, the relevant question now is whether lymphadenectomy in patients with clinically node-negative ICC is beneficial. To date, only 1 study investigated this issue using preoperative findings. Further, our propensity score–matching analysis allowed for a direct comparison of the 2 groups with very similar clinical settings. Based on these advantages, the present

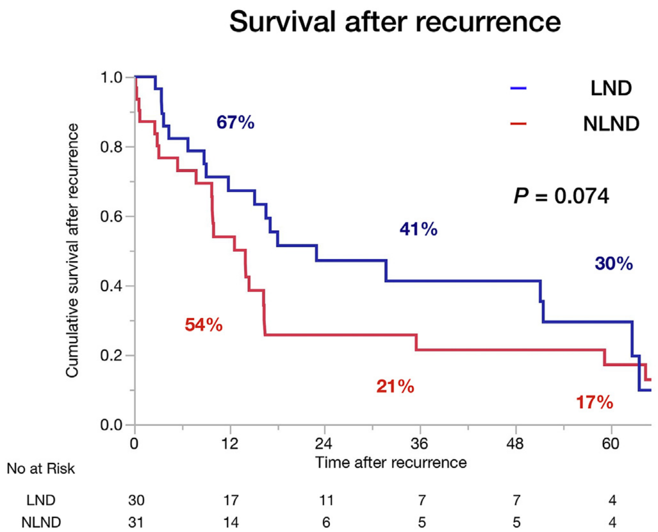

Fig 4. Survival after recurrence of patients with recurrent ICC in the matched cohort.

study demonstrated that lymphadenectomy was associated with survival benefit in patients with clinical node-negative ICC.

Our results support recommending routine lymphadenectomy for clinical node-negative ICC. Despite demonstrating the benefit of lymphadenectomy on long-term survival in our series, the present study cannot clearly answer why lymphadenectomy has prognostic importance. The explanation of the results of this study can be multifactorial. First, better use of adjuvant chemotherapy based on pathologic findings might affect the results. Some studies reported that adjuvant chemotherapy was associated with better long-term outcomes in patients with ICC with pathologic LN metastases, as mentioned in many previous studies.[5,33] Although a true statistical significance was not reached ($P = .181$), more patients in the LND group underwent adjuvant therapy than those in the NLND group (significance was not reached). Second, local control of the perihepatic area might contribute to better DFS ($P = .042$) and survival after resection ($P = .074$). Patients who do not undergo lymphadenectomy are exposed to a risk of LN recurrence in the perihepatic area, which may have been present at the time of resection or may have newly developed from a recurrent ICC. In fact, LN metastasis in the perihepatic area may cause obstructive jaundice, which is difficult to manage[34] and which would support the role of lymphadenectomy at the time of resection despite the absence of clinically positive nodes. A limited number of patients were followed by each tertiary hepatobiliary center after recurrence, which complicates collection of more detailed data. Finally, radical surgery and lymphadenectomy itself might have an undetermined effect to prolong OS and DFS in this subgroup of patients despite there being no rational data to support this hypothesis. Collectively, multifactorial reasons might affect the results, and a much larger sample size is required to explore plausible reasons.

Currently, the importance of adjuvant therapy for ICC is increasingly supported by a high level of evidence[35,36] and may become a standard practice for all ICCs in the near the future. If the role of lymphadenectomy is only to ensure accurate staging, lymphadenectomy would be meaningless. The results of this present study, however, suggest the possibility of some prognostic effect of lymphadenectomy other than ensuring staging. Therefore, we recommend routine lymphadenectomy even in the era of adjuvant strategy.

The present study had a number of limitations. First, the retrospective nature of the multi-institutional study introduced some unavoidable bias (eg, different imaging modalities or different drugs and different evaluated variables, etc.) and difficulty with data collection. We retrieved data that could be assessed from each institutional database as much as possible. Further, collecting detailed data after recurrence was difficult because the 3 institutions were tertiary hospitals. The second limitation is the issue of extent of lymphadenectomy. Although the eighth American Joint Committee on Cancer staging system recommends $\geq$6 LNs to be harvested, the indications for the extent of lymphadenectomy during the study period were left to the discretion of the surgeons.[21] At least, the hepatoduodenal ligament was skeletonized in the LND group among the 3 hospitals, and the results of this present study may be associated with the effect of local control of this area. The prognosis of patients with ICC who did or did not undergo lymphadenectomy was similar between the Japanese and French institutions (Fig 2); therefore, the extent of lymphadenectomy has limited influence. Indeed, it should be noted that the appropriate extent of lymphadenectomy for ICC still remains undetermined. Only a randomized controlled study could solve this issue, and we believe the data of this present study provides the rationale to conduct such study. Last, our model of propensity score matching itself has some limitations. Although propensity score matching allows for the creation of a comparable study population, the sample size is decreased. Although this model is statistically valid, it was only concerned with the evaluated variables; therefore, it could not account for the influence of variables that could not be evaluated in this study. For example, CA19-9 is well known as a prognostic factor in ICC as well as a risk factor for LN metastasis; however, complete data for such tumor markers were not available in this study population.

In conclusion, lymphadenectomy seems to be associated with better long-term outcomes in patients with clinical node-negative ICC. Our data may support routine lymphadenectomy for node-negative ICC with the objective of achieving better long-term outcomes.

Funding/Support

The authors have indicated that they have no funding regarding the content of this article.

Conflict of interest/Disclosure

The authors have indicated that they have no conflicts of interest regarding the content of this article.

Acknowledgments

We would like to thank all the people in Beaujon Hospital, Kyoto University Hospital, and Paul-Brousse Hospital who encouraged us to conduct this international study.

References

1. Bridgewater J, Galle PR, Khan SA, et al. Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. *J Hepatol*. 2014;60:1268–1289.
2. Ribero D, Pinna AD, Guglielmi A, et al. Surgical approach for long-term survival of patients with intrahepatic cholangiocarcinoma: A multi-institutional analysis of 434 patients. *Arch Surg*. 2012;147:1107–1113.
3. Mavros MN, Economopoulos KP, Alexiou VG, Pawlik TM. Treatment and prognosis for patients with intrahepatic cholangiocarcinoma: Systematic review and meta-analysis. *JAMA Surg*. 2014;149:565–574.
4. de Jong MC, Nathan H, Sotiropoulos GC, et al. Intrahepatic cholangiocarcinoma: An international multi-institutional analysis of prognostic factors and lymph node assessment. *J Clin Oncol*. 2011;29:3140–3145.
5. Weber SM, Ribero D, O'Reilly EM, Kokudo N, Miyazaki M, Pawlik TM. Intrahepatic cholangiocarcinoma: Expert consensus statement. *HPB (Oxford)*. 2015;17:669–680.

6. Morine Y, Shimada M. The value of systematic lymph node dissection for intrahepatic cholangiocarcinoma from the viewpoint of liver lymphatics. *J Gastroenterol*. 2015;50:913–927.
7. Adachi T, Eguchi S, Beppu T, et al. Prognostic impact of preoperative lymph node enlargement in intrahepatic cholangiocarcinoma: A multi-institutional study by the Kyushu Study Group of Liver Surgery. *Ann Surg Oncol*. 2015;22:2269–2278.
8. Zhang XF, Chen Q, Kimbrough CW, et al. Lymphadenectomy for intrahepatic cholangiocarcinoma: Has nodal evaluation been increasingly adopted by surgeons over time? A national database analysis. *J Gastrointest Surg*. 2018;22:668–675.
9. Bagante F, Spolverato G, Weiss M, et al. Assessment of the lymph node status in patients undergoing liver resection for intrahepatic cholangiocarcinoma: The new eighth edition AJCC staging system. *J Gastrointest Surg*. 2018;22:52–59.
10. Jutric Z, Johnston WC, Hoen HM, et al. Impact of lymph node status in patients with intrahepatic cholangiocarcinoma treated by major hepatectomy: A review of the National Cancer Database. *HPB (Oxford)*. 2016;18:79–87.
11. Sotiropoulos GC, Bockhorn M, Sgourakis G, et al. R0 liver resections for primary malignant liver tumors in the noncirrhotic liver: A diagnosis-related analysis. *Dig Dis Sci*. 2009;54:887–894.
12. Endo I, Gonen M, Yopp AC, et al. Intrahepatic cholangiocarcinoma: Rising frequency, improved survival, and determinants of outcome after resection. *Ann Surg*. 2008;248:84–96.
13. Wang K, Zhang H, Xia Y, Liu J, Shen F. Surgical options for intrahepatic cholangiocarcinoma. *Hepatobiliary Surg Nutr*. 2017;6:79–90.
14. Bagante F, Spolverato G, Weiss M, et al. Surgical management of intrahepatic cholangiocarcinoma in patients with cirrhosis: Impact of lymphadenectomy on peri-operative outcomes. *World J Surg*. 2018;42:2551–2560.
15. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. *PLoS Med*. 2007;4(10):e296.
16. Farges O, Fuks D, Boleslawski E, et al. Influence of surgical margins on outcome in patients with intrahepatic cholangiocarcinoma: A multicenter study by the AFC-IHCC-2009 study group. *Ann Surg*. 2011;254:824–829.
17. Sakamoto Y, Kokudo N, Matsuyama Y, et al. Proposal of a new staging system for intrahepatic cholangiocarcinoma: Analysis of surgical patients from a nationwide survey of the Liver Cancer Study Group of Japan. *Cancer*. 2016;122:61–70.
18. Ferrer R. Lymphadenopathy: Differential diagnosis and evaluation. *Am Fam Physician*. 1998;58:1313–1320.
19. Ganeshalingam S, Koh DM. Nodal staging. *Cancer Imaging*. 2009;9:104–111.
20. Yoh T, Hatano E, Seo S, et al. Preoperative criterion identifying a low-risk group for lymph node metastasis in intrahepatic cholangiocarcinoma. *J Hepatobiliary Pancreat Sci*. 2018;25:299–307.
21. Amin MB, Edge S, Greene F, et al. *AJCC Cancer Staging Manual*. 8th ed. New York: Springer; 2017.
22. Spolverato G, Kim Y, Ejaz A, et al. Conditional probability of long-term survival after liver resection for intrahepatic cholangiocarcinoma: A multi-institutional analysis of 535 patients. *JAMA Surg*. 2015;150:538–545.
23. Yoh T, Hatano E, Nishio T, et al. Significant improvement in outcomes of patients with intrahepatic cholangiocarcinoma after surgery. *World J Surg*. 2016;40:2229–2236.
24. Strasberg SM. Nomenclature of hepatic anatomy and resections: A review of the Brisbane 2000 system. *J Hepatobiliary Pancreat Surg*. 2005;12:351–355.
25. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240:205–213.
26. Intraobserver and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C: The French METAVIR Cooperative Study Group. *Hepatology*. 1994;20:15.
27. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. *Pharm Stat*. 2011;10:150–161.
28. Sposito C, Battiston C, Facciorusso A, et al. Propensity score analysis of outcomes following laparoscopic or open liver resection for hepatocellular carcinoma. *Br J Surg*. 2016;103:871–880.
29. Kim DH, Choi DW, Choi SH, Heo JS, Kow AW. Is there a role for systematic hepatic pedicle lymphadenectomy in intrahepatic cholangiocarcinoma? A review of 17 years of experience in a tertiary institution. *Surgery*. 2015;157:666–675.
30. Kim SH, Han DH, Choi GH, Choi JS, Kim KS. Oncologic impact of lymph node dissection for intrahepatic cholangiocarcinoma: A propensity score-matched study. *J Gastrointest Surg*. 2018;23:538–544.
31. Hu J, Chen FY, Zhou KQ, et al. Intrahepatic cholangiocarcinoma patients without indications of lymph node metastasis not benefit from lymph node dissection. *Oncotarget*. 2017;8:113817–113827.
32. Shimada K, Sano T, Nara S, et al. Therapeutic value of lymph node dissection during hepatectomy in patients with intrahepatic cholangiocellular carcinoma with negative lymph node involvement. *Surgery*. 2009;145:411–416.
33. Miura JT, Johnston FM, Tsai S, et al. Chemotherapy for surgically resected intrahepatic cholangiocarcinoma. *Ann Surg Oncol*. 2015;22:3716–3723.
34. Nichols SD, Albert S, Shirley L, et al. Outcomes in patients with obstructive jaundice from metastatic colorectal cancer and implications for management. *J Gastrointest Surg*. 2014;18:2186–2191.
35. Primrose JN, Fox RP, Palmer DH, et al. Capecitabine compared with observation in resected biliary tract cancer (BILCAP): A randomised, controlled, multicentre, phase 3 study. *Lancet Oncol*. 2019;20:663–673.
36. Kobayashi S, Nagano H, Tomokuni A, et al. A prospective, randomized phase II study of adjuvant gemcitabine versus S-1 after major hepatectomy for biliary tract cancer (KHBO 1208): Kansai Hepato-Biliary Oncology Group. *Ann Surg*. 2018. https://doi.org/10.1097/SLA.0000000000002865 [Epub ahead of print].