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Clinical implication of tumor site in terms of node metastasis for intrahepatic cholangiocarcinoma

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ABSTRACT

Background: The clinical implication of lymph node (LN) dissection of intrahepatic cholangiocarcinoma (ICCA) is still controversial, and LN metastasis (LNM) based on tumor site has not been confirmed yet.
Methods: Patients who underwent curative-intent surgery at 10 tertiary referral centers were identified and divided into peripheral (PP) and near second confluence level tumor (NC) groups on the basis of the distance from the second confluence and oncological outcomes were compared.
Results: Of 179 patients, 121 patients with LND were divided into the NC (n = 89) and PP groups (n = 32) on the basis of 4.5 cm from the second confluence. NC group showed higher LNM rate than PP group (46.1 vs 21.9%, p = 0.016) and NC was a risk factor for LNM (odds ratio: 4.367; 95% confidence interval: 1.234–15.453, p = 0.022). The 5-year overall survival (OS) rate (38.0% vs. 27.8%, p = 0.777) and recurrence-free survival (RFS) rates (22.8% vs. 25.8%, p = 0.742) showed no differences between the PP and NC groups. In the NC group, N1 patients showed worse 5-year OS (12.7% vs 39.0%, p = 0.004) and RFS (8.8% vs 28.6%, p = 0.004) than the N0 patients. In the PP group, discordant results in 5-year OS (48.9% vs. 50.0%, p = 0.462) and RFS (41.3% vs. 0%, p = 0.056) were found between the N0 and N1 patients.
Conclusion: The NC group was an independent risk factor for LNM and LNM worsened prognosis in NC group for ICCA. In the PP group, LND should not be omitted because of high LNM rate and insufficient oncologic evidence.

Introduction

Intrahepatic cholangiocarcinoma (ICCA) is a rare gastrointestinal malignant disease [1]. It is the second most common liver cancer and constitutes 10–20% of all liver cancers, but it accounts

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for only 10% of bile duct cancers [2]. The incidence of ICCA in Korea has increased in recent years and is second only to that in Thailand globally [1,2]. Surgery is the mainstay for curative treatment [3]. As ICCA tumors are large and located around the liver hilum, more than half of patients require major hepatectomies and more than a quarter of the patients require hepaticojejunostomies. Lymph node metastases (LNM) are found in 30–40% of ICCA patients and are well-known prognostic factors for survival [4,5]. Furthermore, recent guidelines recommend lymph node dissection (LND) for evaluating LNM [2]. However, the clinical use of LND is still controversial. Investigators who favor LND insist that LND could prevent tumor spread through the perineural space, prevent potential micrometastatic foci even in patients without LNM, bypass inadequate information due to insufficient preoperative imaging, and be used for preemptive removal of frequent metastatic sites [3,6–8]. However, clinicians who do not favor the use of LND insist that LNM imply systemic disease and that LND does not affect survival in patients with or without LNM [9–11]. Some investigators have shown that peripherally located small-sized tumors have lower rates of LNM than centrally located tumors [12]. Furthermore, they insist that surgeons do not need to perform LND for peripheral ICCA because of the low incidence of LNM in peripheral ICCAs [13–15]. However, these previous studies included only a small number of patients. The aim of the present study was to compare patterns of LNM according to the distance from the second confluence and to evaluate the clinical use of LND in peripheral and centrally located ICCAs.

Methods

Patients and study design

Patients who underwent curative-intent surgery for ICCA in 10 tertiary referral centers between January 2000 and December 2017 were identified. Patients with hilar cholangiocarcinomas, or those with R2 resections were excluded. The patients underwent major or minor liver resections with LND and bile duct reconstructions in accordance with the tumor invasion of the proximal bile duct margin. We divided the patients into a peripheral (PP) group and a near second confluence tumor (NC) group on the basis of their preoperative computed tomography (CT) results. As three-dimensional (3-D) reconstruction was not available in all of the 10 centers, we calculated the distance from the level of the second confluence using the Pythagorean theorem. The straight-line distance from the second bifurcation of the portal vein to the center of the tumor was obtained using the number of CT slices, and the straight-line distance from the center of the tumor to the virtual point was obtained. We used these two distances and the Pythagorean theorem to calculate the linear distance from the second branch of the portal vein to the tumor mass. The 3-D linear distance of the tumor was then obtained by subtracting the radius of the tumor (Supplementary Fig. 1). We compared perioperative and oncological outcomes between the PP and NC tumor groups.

We collected clinical data using patient medical records and used the following parameters in our analyses: preoperative data (age, sex, body mass indices [BMI], American Society of Anesthesiologists [ASA] scores, preoperative CT imaging results, and tumor markers); intraoperative data (gross type, extent of resections, operation times, intraoperative transfusions, and estimated blood loss); pathological data (histologic grades, node metastases, and the presence of lymphovascular or perineural invasions); and postoperative data (hospital stays, complications, 30-day mortality, recurrences, and survival). Informed consent was obtained from the patients before surgery. This study was approved by the institutional review board of each institution.

Statistical analyses

Data were expressed as mean ± standard deviations. The χ [2] test was used to compare categorical variables, and the Student's *t*-test was used to compare continuous variables among subgroups. Survival rates were calculated using the Kaplan-Meier method and compared between the two groups using the log-rank test. The multivariable Cox proportional hazards model was used to determine prognostic factors for disease-related deaths. In all the analyses, a *P* value of <0.05 (two-sided) was considered statistically significant. SPSS version 22.0 (SPSS Corp., Chicago, IL, USA) was used in all the analyses.

Results

Patients' characteristics

Of 179 patients, 55 who did not undergo LND (Nx) and 3 with incomplete medical records were excluded. In this study, 121 patients with a mean age of 63.7 years were enrolled. All the patients had Child-Pugh class A (117, 96.7%) or B (4, 3.3%). The mean indocyanine green retention ratio after 15 min was 8.9%. Tumors were located in the left and right lobes in 57 (47.1%) and 63 patients (52.1%), respectively. The mean tumor size was 5.1 cm, and the distance from the second confluence was 3.1 cm. The patients underwent open (110, 90.9%) and laparoscopic procedures (11, 9.1%), and 18 (14.9%) and 102 patients (84.3%) underwent minor and major hepatectomies, respectively. Twelve patients (9.9%) required hilar resections, including hepaticojejunostomies. Multiple tumors were found in 8 patients (6.6%), and 48 patients (39.7%) had pathology reports indicating node metastases. The postoperative severe complication rate was 4.5% which was classified IIIb or more using Clavien-Dindo system, and the mean hospital stay was 18.4 days (Table 1).

Comparison of LNM according to tumor site

We compared LNM between the PP (n = 32) and NC groups (n = 89) and found significantly higher node metastases in tumors < 4.5 cm from the level of the second confluence than in peripheral tumors (46.1% vs. 21.9%, p = 0.016; Supplementary Table 1). We performed a multivariate analysis to determine if the distance from the second confluence was an independent risk factor for node metastases. Carcinoembryonic antigen (CEA) levels of >5 ng/ml (p = 0.018), lymphovascular invasions (p < 0.001), and perineural invasions (p = 0.024) were related to node metastases in the univariate analysis. In the multivariate analysis, distance (<4.5 cm) from the second confluence (odds ratio [OR]: 4.367; 95% confidence interval [CI]: 1.234–15.453, p = 0.022), and CEA levels of >5 ng/ml (OR: 3.384, p = 0.028; 95% CI: 1.143–10.016) were associated with lymph node metastases (Table 2).

In the subgroup analyses, we considered additional factors such as tumor size, left- or right-sided tumors, or gross tumor type. In the solitary tumor groups of <5 or >5 cm in size, a significant difference in node metastasis was found between the PP and NC groups. In the left-sided tumor group, tumors 4 cm from the second confluence showed significantly higher node metastases than the PP group (59.1% vs. 31.6%, p = 0.045). The mass-forming tumor groups showed a higher node metastasis rate in the NC group than in the PP group (48.6% vs. 24.3%, p = 0.015; Supplementary Table 2).

Perioperative outcomes between the PP and NC tumor groups

On the basis of a 4.5-cm distance from the second confluence, we compared perioperative and oncological outcomes between the

Table 1
Comparison of perioperative outcomes between near 2nd confluence and peripheral tumor groups in patients with intrahepatic cholangiocarcinoma.

	All patients (N = 121)	2nd confluence < 4.5 cm (N = 89)	2nd confluence≥4.5 cm (N=32)	p-value
Age	63.7 ± 9.5	63.7 ± 8.4	63.5 ± 12.2	0.907
Males	80 (66.1)	59 (66.3)	21 (65.6)	0.945
ASA score (I, II/III)	27 (22.3)/88 (72.7)/7 (5.0)	17(17.1)/67(75.3)/5(5.6)	10(31.3)/21(65.6)/1(3.1)	0.341
Child-Pugh score (A/B/C)	117 (96.7)/4 (3.3)/0	87(97.8)/2(2.2)/0	30(93.8)/2(6.3)/0	0.277
ICG R15%	8.9 ± 5.3	9.3 ± 5.5	8.0 ± 4.8	0.364
CEA (ng/ml)	24.7 ± 115.2	24.6 ± 126.3	24.8 ± 75.6	0.995
CA19-9 (U/ml)	1,130.9 ± 3,212.4	1,386.6 ± 3,639.1	454.7 ± 1,455.2	0.054
Distance from 2nd confluence	3.1 ± 2.6	1.9 ± 1.3	6.4 ± 2.3	<0.001
Major liver resection	105 (84.3)	80 (89.9)	22 (71.0)	0.011
Hepaticojejunostomy	12 (9.9)	12 (17.4)	0	0.015
Operation time (min)	352.4 ± 116.8	369.3 ± 116.9	306.6 ± 105.2	0.009
Estimated blood loss (ml)	941.9 ± 955.9	1,045.6 ± 1,073.3	689.0 ± 508.5	0.075
Intraoperative transfusion	58 (47.9)	46 (52.9)	12 (37.5)	0.137
Tumor Size (cm)	5.1 ± 2.1	5.0 ± 2.1	5.2 ± 2.3	0.656
Gross type (MF/PI/IG)	108 (89.2)/5(4.1)/6(5.0)	78(87.5)/5(5.7)/5(5.7)	30(96.8)/0/1(3.2)	0.456
R1 resection	12 (9.9)	8 (9.0)	1(3.1)	0.303
T stage (1a/1b/2/3/4) (8th AJCC staging system)	34 (28.1)/32 (26.4)/24 (19.8)/28 (23.1)/3 (2.5)	24(27.6)/25(28.7)/14(16.1)/21(24.1)/3(3.4)	9(28.1)/6(18.8)/10(31.3)/7(21.9)/0	0.318
N stage (0/1) (8th AJCC staging system)	73 (60.3)/48 (39.7)	48 (53.9)/41 (46.1)	25 (78.1)/7 (21.9)	0.016
Lymphatic invasion	69 (57)	47 (55.3)	22 (71.0)	0.128
Perinueral invasion	43 (35.5)	34 (54.0)	9 (34.6)	0.097
Cell differentiation				
WD/MD/PD	18(14.8)/51(42.1)/28(23.1)	16(21.6)/37(50.0)/18(24.3)	2(7.4)/14(51.9)/10(37.0)	0.455
Postoperative complications	52 (43)	35 (39.3)	17 (53.1)	0.176
Severe complication (CD ≥ IIIb)	4 (4.5)	4 (4.5)	0	0.572
Hospital stay (days)	18.4 ± 13.8	18.9 ± 14.1	17.1 ± 13.3	0.546
30d mortality	2 (1.6)	1 (1.1)	1 (3.4)	0.446
Adjuvant therapy	79 (65.3)	58 (65.2%)	21 (65.6%)	0.963
Recurrence pattern				
Intrahepatic	31 (25.6)	23 (25.8)	8 (25.0)	1.000
Node	19 (15.7)	16 (18.0)	3 (9.4)	0.396
Systemic	30 (24.7)	23 (25.8)	7 (21.9)	0.812

ICG: Indocyanine green, ASA: American Society of Anesthesiologists, CEA: carcinoembryonic antigen, CA19-9: carbohydrate antigen 19–9, MF: mass forming type, PI: periductal infiltrative type, IG: intraductal growth type, AJCC: American Joint Committee on Cancer, WD: well differentiated, MD: moderately differentiated, PD: poorly differentiated, CD: Clavien-Dindo classification.

Table 2
Risk Factors for lymph node metastasis in patients with lymph node dissections.

Variable	Univariate Analysis			Multivariable Analysis	
	Subgroup (n)	p-value	HR	95% CI	p-value
Age (years)	<70 (42) ≥70 (82)	0.535			
Sex	Male (82) Female (42)	0.087			
ASA score	I (27) II/III (97)	0.102			
CEA (ng/ml)	≥5 (46) <5 (63)	0.018	3.384	1.143–10.016	0.028
CA19-9 (U/ml)	<37 (55) ≥37 (61)	0.373			
Multiple tumor	Yes (8) No (116)	0.531			
Lymphatic invasion	Yes (71) No (48)	<0.001	1.722	0.527–5.623	0.368
Microvascular invasion	Yes (36) No (80)	0.324			
Perineural invasion	Yes (44) No (48)	0.024	2.737	0.975–7.677	0.056
Tumor size (cm)	<5 (65) ≥5 (57)	0.988			
Near 2nd confluence <4.5 cm	Yes (89) No (32)	0.016	4.367	1.234–15.453	0.022

HR: hazard ratio, CI: confidence interval, ASA: American Society of Anesthesiologists, CEA: carcinoembryonic antigen, CA19-9: carbohydrate antigen 19-9.

PP and NC groups. No significant differences in patient characteristics and preoperative data, with the exception of the distance from the second confluence (1.9 cm vs. 6.4 cm, p < 0.001). The operative data showed that the NC group required more frequent major hepatectomies (89.9% vs. 71.0%, p = 0.011), hepaticojejunostomies (17.4% vs. 0%, p = 0.015), and use of the Pringle

maneuver (40.5% vs. 18.8%, p = 0.028) than the PP group. The NC group also required longer operative times than the PP group (369.3 min vs. 306.6 min, p = 0.009). No other significant differences in pathologic and postoperative data were found between the two groups (Table 1).

Oncological outcomes in the patients with PP and NC groups

The median follow-up period was 22.0 months. The 5-year overall survival (OS) and recurrence-free survival (RFS) rates were 42.5% and 27.8%, respectively. No significant differences in 5-year OS (32.7% vs. 43.6%, p = 0.364) and RFS (23.1% vs. 28.4%, p = 0.453) rates were found between the NC and PP groups. We investigated the oncological benefit of LND including 55 Nx patients. No significant differences in 5-year OS (53.6% vs. 33.5%, p = 0.058) and RFS rates (24.2% vs. 24.4%, p = 0.191) were found between the Nx patients and those with LND. We also compared oncological outcomes on the basis of LN status categories (N0, N1, and Nx). The N1 group showed lower 5-year OS and RFS rates than the Nx (OS: 18.7% vs. 53.6%, p = 0.003; RFS: 0% vs. 24.4%, p = 0.001) and N0 groups (OS: 18.7% vs. 36.8%, p = 0.007, RFS: 0% vs. 34.0%, p = 0.001). However, we found no significant differences in 5-year OS (53.6% vs. 36.8%, p = 0.385) and RFS rates (24.4% vs. 34.0%, p = 0.933) between the Nx and N0 groups. The prognostic factors for survival were CEA levels of ≥5 ng/ml (hazard ratio [HR]: 2.758, p = 0.004; 95% CI: 1.374–5.536) and lymphovascular invasions (HR: 3.488, p = 0.021; 95% CI: 1.203–10.118).

Owing to the possibility of bias in the Nx patients, oncological outcomes were analyzed for the patients with LND. The 5-year OS (38.0% vs. 27.8%, p = 0.777) and RFS rates (22.8% vs. 25.8%, p = 0.742) showed no significant differences between the PP and NC groups (Fig. 1). In the NC group, the N0 patients showed better 5-year OS (39.0% vs. 12.7%, p = 0.004) and RFS rates (28.6% vs. 8.8%, p = 0.004) than the N1 patients (Fig. 2). However, in the PP group, no significant differences in 5-year OS (48.9% vs. 50.0%, p = 0.462) and RFS rates (41.3% vs. 0%, p = 0.056) were found between the N0 and N1 patients (Fig. 3). Seventy-two patients (57.1%) had postoperative recurrences. The recurrence patterns showed no significant difference between the NC and PP groups and included intrahepatic (25.8% vs. 25.0%, p = 1.000), systemic (25.8% vs. 21.9%, p = 0.812), and node recurrences (18.0% vs. 9.4%, p = 0.396).

Discussion

ICCA is defined as intrahepatic bile duct cancer distal from the second confluence [4]. The incidence in Eastern countries is 2.25–85 per 0.1 million persons, which is higher than the incidence in Western countries (0.3–1.67 per 0.1 million persons). Furthermore, the incidence of ICCAs has been increasing [2]. While surgery is the mainstay for curative treatments, surgeons need to take into account that remnant liver because major hepatectomies occur in 49–78% of patients and bile duct resections with hepaticojejunostomies occur in 21–29% of patients [3,7]. The median survival was 26 months, and the 5-year survival rate was reported to be 15–40%. Thirty to 70% of patients experienced LNM [4]. Recent guidelines recommend that LND should be included to accurately evaluate the staging and decisions regarding adjuvant chemotherapy [2].

This study investigated the different patterns of LNM and the possibility of omitting LND for ICCA surgery in the NC and PP groups. We showed that the incidence of LNM was higher in the NC group than in the PP group and was an independent risk factor. This pattern is especially demonstrated in mass-forming ICCA. The NC group showed more frequent major hepatectomy, including hepaticojejunostomy, and longer operation time than the PP group. The patients with N1 had worse survival than those with N0, and the survival curve of the Nx group was similar to that of the N0 group. In the patients with LND, LNM was related to better prognosis in the NC group. However, the prognosis of the PP group was not related to LNM.

Tumors located near the second confluence was an independent risk factor for high LNM rates, as compared with those located at the periphery. In the NC group, the possibility of metastases was higher than that in the PP group because the adjacent hepatic

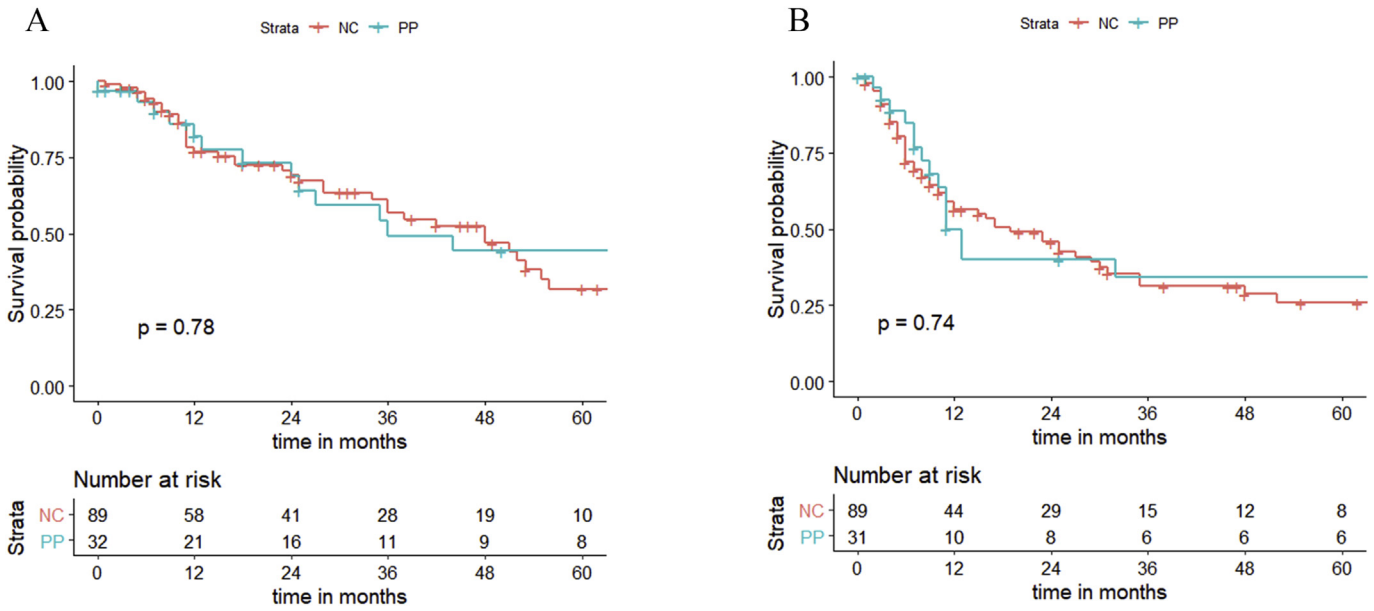

Fig. 1. Comparison of the overall survival and recurrence-free survival rates of the patients between peripheral and near second confluence tumor groups.
The patients showed no significant differences in the 5-year overall (38.0% vs. 27.8%, p = 0.777) and recurrence-free survival rates (22.8% vs. 25.8%, p = 0.742) between peripheral and near second confluence tumor groups.

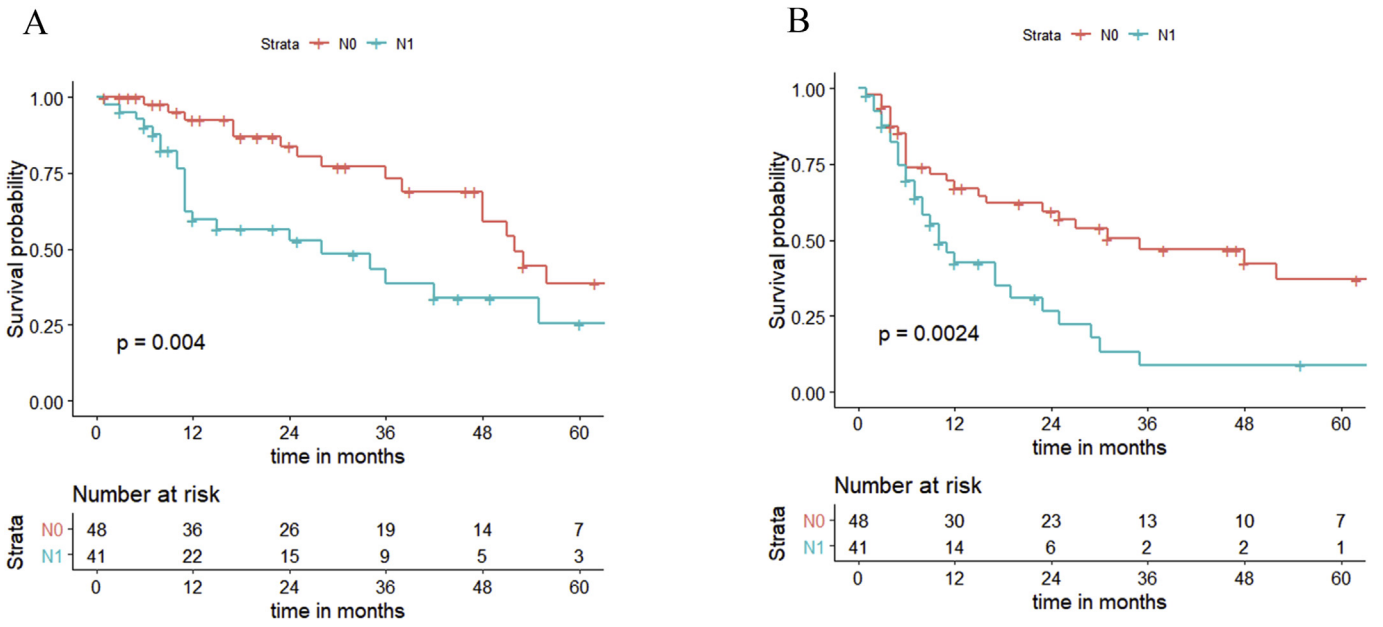

Fig. 2. Comparison of the overall survival and recurrence-free survival rates of the patients based on node metastases in the near second confluence group.
The patients with node metastases showed lower 5-year overall (39.0% vs. 12.7%, $P = 0.004$) and recurrence-free survival rates (28.6% vs. 8.8%, $p = 0.004$) than those without node metastases.

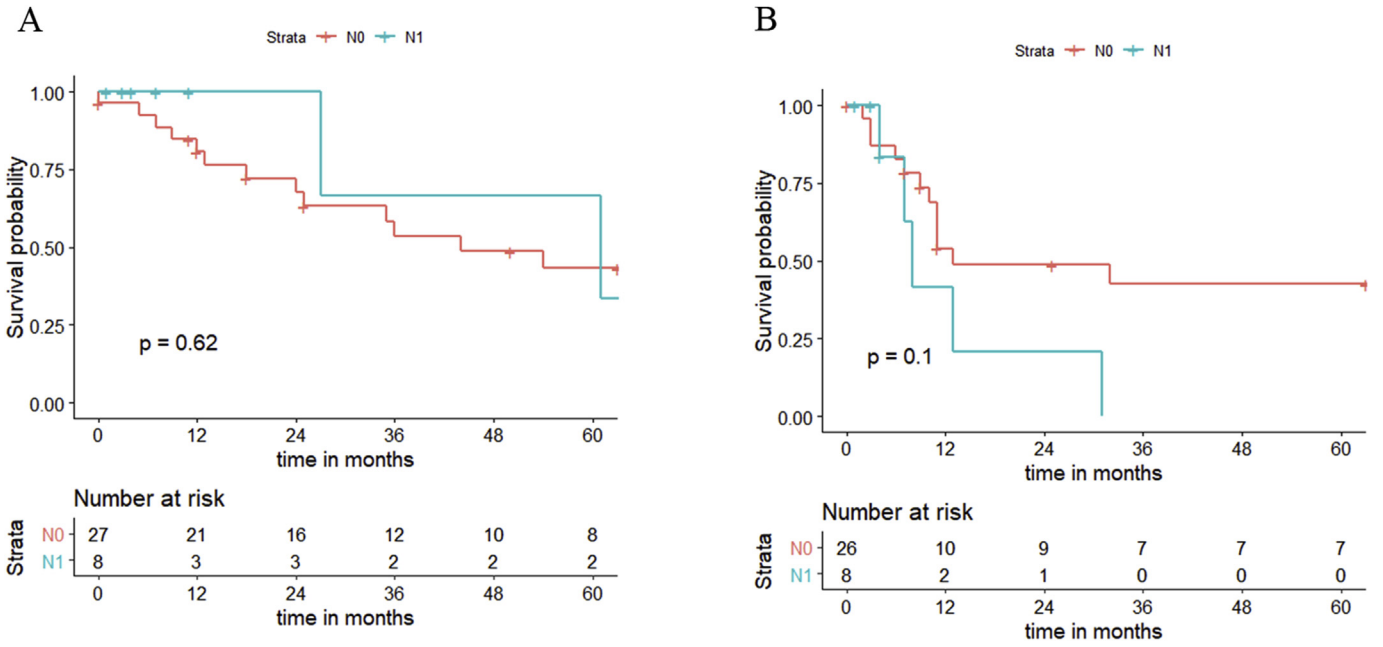

Fig. 3. Comparison of the overall and recurrence-free survival rates of the patients based on node metastases in the peripheral tumor group.
The 5-year overall (48.9% vs. 50.0%, $P = 0.462$) and recurrence-free survival rates (41.3% vs. 0%, $p = 0.056$) were not significantly different between the N0 and N1 groups.

artery and portal veins cluster as they approach the liver hilum [16,17]. Therefore, surgical treatment included a higher proportion of bile duct resections with hepaticojejunostomies in the NC group than in the PP group. Recent studies discriminated perihilar and peripheral ICCAs on the basis of distinct precursor cells. The characteristics of perihilar ICCA were positive MUC5AC and MUC6 immunophenotypes, SMAD4 mutation, and the presence of the KRAS gene [18,19]. Although histological comparisons were absent between the NC and PP groups in this study, the groups had clinical similarities such as lower LNM, gross appearance, and higher intrahepatic metastases [18]. However, tumor growth near the second confluence was not a prognostic factor of survival and recurrence, but was a prognostic factor in LND in this study. Previous studies showed controversial results regarding hilar and peripheral cholangiocarcinomas [20,21]. A recent study compared the prognosis between ICCAs with peripheral and hilar invasions, as in this study, and showed that patients with ICCAs with hilar invasion had worse prognosis than those with ICCAs with both hilar and

peripheral invasions [22]. However, the NC group in this study included 17% patients with ICCAs with hilar invasion, and the characteristics of these patients were different from those in the previous study. Furthermore, multivariate analyses revealed that the tumor location did not affect long-term outcome, and this study showed similar results [22]. High CEA levels and lymphovascular invasion, and not tumor location, were prognostic factors in all the patients with ICCA.

This study showed no oncologic benefit of LND in all patients. However, the survival curves for the Nx group were similar to those for the N0 group and not the N1 group. The patients who belonged to the Nx group were more likely to have N0. Surgeons could select LND on the basis of node enlargement observed in the preoperative imaging studies in this study. This could be considered a potential bias because the accuracy of LNM based on preoperative imaging studies is approximately 60%, and micrometastatic foci may be present even in patients without LNM [12,23]. A prospective registry for patients with ICCA who undergo hepatectomy and LND may provide a solution to this clinical question. The current guideline recommends LND as an essential procedure for accurate staging of resectable ICCAs [2].

This study showed that the clinical implications of LND differ between the NC and PP groups in terms of oncological outcomes. In the NC group, LNM worsened prognosis because of potential tumor spread along the liver hilum [24]. The surgical strategy for R0 resection is similar to that for hilar cholangiocarcinomas, including major hepatectomies, LNDs, vascular reconstructions, and bile duct resections [25,26]. However, LND is controversial in PP group. Previous investigators showed that intrahepatic recurrence was more predominant than node metastasis [14], insisting that routine LND was not useful for the peripheral tumor group especially mass forming type tumor less than 5 cm [13,14]. In this study, we found evidence to support the previous results. The patients in the PP group showed similar oncological outcomes of LNM. Although we suggest that LND is ineffective for PP tumors, some limitations must be mentioned. The analyses of data from a small number of patients in the PP group may have been inadequately powered to detect differences. Furthermore, all the patients with N1 experienced recurrence in contrast to N0 patients, who had a lower recurrence rate of 60%; however, this difference did not reach statistical significance. Previous studies suggested the omission of LND in patients with a <5-cm-mass-forming ICCA [13,15]. However, this study showed that the LNM rates of the PP group was 22% regardless of the size and gross type. Gallbladder cancer with perimuscular connective tissue invasion showed an LNM rate of >20%, and the standard treatment procedures included LND [27]. Current evidence supports the oncological benefit of adjuvant chemotherapy in patients with LNM, and identification of LNM in ICCA is important as stated in the guideline [2,22,28]. Therefore, the evidence to support the omission of LND for peripheral ICCA is insufficient in this study, and a large-scale study involving a large number of patients may provide a definitive conclusion on this issue.

This study has several limitations. As ICCA is a rare disease, the collected patient data were limited. Potential bias may exist because this was a retrospective study. One-third of the patients did not undergo LND, so the clinical significance of LND could not be interpreted accurately. Central pathology reviews were not performed because of strict regulations at each institution.

In conclusion, the NC group was an independent risk factor for LNM, even when considering other factors. LND is essential for patients within the NC group, and LNM worsened prognosis. There is insufficient evidence to discuss the omission of LND in PP groups so far.

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Declaration of competing interest

All authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.11.511.

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