



Therapeutic Index Associated with Lymphadenectomy Among Patients with Intrahepatic Cholangiocarcinoma: Which Patients Benefit the Most from Nodal Evaluation?

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ABSTRACT

Background. Although lymph node metastasis (LNM) is an important prognostic indicator for patients with intrahepatic cholangiocarcinoma (ICC), the benefit and indication for lymphadenectomy remain unclear.

Methods. Patients diagnosed with ICC between 1990 and 2016 were identified in the international multi-institutional

dataset. To determine the survival benefit from lymphadenectomy, the therapeutic index was calculated by multiplying the frequency of LNM in a particular group of patients by the 3-year cancer-specific survival (CSS) rate of patients with LNM in that subgroup.

Results. Among 471 patients who met the inclusion criteria, approximately half had LNM ($n = 205$, 43.5%). The median number of resected and metastatic LNs were 4 [interquartile range (IQR) 2–8] and 0 (IQR 0–1), respectively. Three-year CSS in the entire cohort was 29.9%, reflecting a therapeutic index value of 13.0. The therapeutic index was lower among patients with major vascular invasion (5.4), preoperative carcinoembryonic antigen (CEA) > 5.0 (8.2), and LNM in areas other than the hepatoduodenal ligament (5.2). Of note, a therapeutic index difference of more than 10 points was noted only when examining the number of LNs harvested [1–2 (4.1) vs. 3–6 (16.1) vs. ≥ 7 (17.8)].

Conclusion. The survival benefit derived from lymphadenectomy was poor among patients with major

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vascular invasion, CEA > 5.0, and LNM in areas other than the hepatoduodenal ligament. Resection of three or more LNs was associated with the highest therapeutic value among patients with LNM.

Intrahepatic cholangiocarcinoma (ICC) is a relatively rare cancer with an increasing incidence in the US over the last three decades.^{1,2} Despite the unfavorable outcomes of patients diagnosed with ICC, surgery remains the mainstay of potentially curative treatment for patients with ICC amenable to resection.³⁻⁷ Appropriate oncologic principles of ICC resection include both complete removal of the tumor as well as a lymphadenectomy. While lymphadenectomy is essential to adequately stage the disease and decrease the risk of locoregional recurrence,^{8,9} the extent of lymphadenectomy and its related therapeutic benefit remain a topic of debate.^{6,10-15} Indeed, an analysis of the Surveillance, Epidemiology, and End Results (SEER) database noted that only one-half of patients had pathological examination of at least one regional lymph node (LN).^{10,11} To this end, data are needed to define the potential therapeutic benefit, as well as identify the group of patients who might benefit the most from LN dissection (LND), to guide treatment planning and improve long-term outcomes.¹⁶

First proposed by Sasako et al., the therapeutic index is a simple metric that aims to determine the survival benefit derived from LND among patients undergoing surgery for gastrointestinal (GI) malignancies.¹⁷ The rationale of this metric is that LND should ideally be performed among patients with a high predicted incidence of LN metastasis and who could, therefore, derive a survival benefit.¹⁷ Although first applied to evaluate the survival benefit of LND among patients with gastric cancer,^{16,18,19} the concept of nodal therapeutic index has also been applied to patients with colorectal cancer.²⁰ In fact, the therapeutic index has been included in the Japanese Classification of Gastric Carcinoma (JCGC), suggesting wide acceptance among certain clinicians.²¹ The concept of LN therapeutic index has not been investigated, applied, or validated among patients with hepatobiliary malignancies. As such, the objective of the current study was to examine the survival benefit of lymphadenectomy among patients undergoing resection for ICC utilizing the therapeutic index. Furthermore, we sought to identify the subgroup of patients most likely to have derived the least versus most benefit from LND at the time of surgery for ICC.

METHODS

Study Population and Data Collection

Patients undergoing surgical resection for ICC between January 1990 and December 2016 were identified in a multi-institutional database incorporating data from 15 tertiary institutions. For the purpose of this study, only patients with histologically confirmed ICC who underwent curative intent liver resection were analyzed. Patients who did not undergo lymphadenectomy were excluded from the analyses, as well as patients with macroscopic positive surgical margins (R2 resection), 30-day mortality after surgery, and missing follow-up data. The Institutional Review Boards of the participating institutions approved this study.

Patient demographic and clinicopathologic data were extracted, including age, sex, race, American Society of Anesthesiologists (ASA) class, the presence of cirrhosis, preoperative serum level of carbohydrate antigen (CA) 19-9 and carcinoembryonic antigen (CEA), type of resection, number of ICCs, tumor size, lymph nodal status, location of LN metastasis (LNM), morphological type (MF: mass-forming; IG: intraductal growth; PI: periductal infiltrating), tumor grade and margin status, major or minor vascular invasion, and the presence of perioperative chemotherapy. Major hepatectomy was defined as the resection of three or more Couinaud segments.²² LN basins were classified into two categories: hepatoduodenal ligament, and other station including celiac and para-aortic LNs. Major vascular invasion was defined as invasion of the first- and second-order branches of the portal vein or hepatic arteries, or as invasion of one or more of the three hepatic veins. In contrast, microvascular invasion was defined as intraparenchymal vascular involvement identified on histological examination.²³

Therapeutic Index

The therapeutic index of lymphadenectomy was calculated by multiplying the frequency of LNM in a particular group of patients by the 3-year cancer-specific survival (CSS) rate of patients with LNM in that subgroup, as previously reported.¹⁸ The therapeutic index was estimated for both clinicopathological and LN-related characteristics, as previously described.¹⁸ The incidence of LNM was calculated by dividing the number of patients with metastatic LN by the total number of patients in this particular subgroup. The 3-year CSS was calculated for each group of patients with metastatic LNs, irrespective of the metastasis to LN stations or number of LNs harvested. In cases where a therapeutic index interval, defined as the difference of the

therapeutic index values between two groups, was more than 10, LND was considered meaningful.^{16,19}

Statistical Analysis

Descriptive statistics were presented as median [interquartile range (IQR)] and frequency (%) for continuous and categorical variables, respectively. Statistical significance was assessed at $\alpha = 0.05$. A logistic multivariable regression model was used to identify independent predictors of LNM. Patients who were alive or had died of a cause other than ICC were censored for analysis of CSS. CSS was defined as the time from the date of first liver resection to the date of death or last follow-up. CSS was calculated by creating Kaplan–Meier curves, and survival was compared using log-rank tests. The association of clinicopathologic variables with CSS was evaluated by using a Cox proportional hazards model. The multivariable model was developed by fitting bivariate generalized estimating equation (GEE) models for each confounder and including the variable in the subsequent stage of analysis if the statistical significance was $p < 0.05$ for the primary outcome.²⁴ All statistical analyses were performed using SPSS version 25 (IBM Corporation, Armonk, NY, USA).

RESULTS

Characteristics of Patients Undergoing Lymphadenectomy

Among 1086 patients, 648 (59.6%) patients were treated in Western hospitals, whereas 438 (40.4%) were treated in Eastern hospitals (electronic supplementary Table S1). In total, 522 patients (48.1%) underwent LND, whereas 564 patients (51.9%) did not (electronic supplementary Fig. S1). Among the 522 patients who underwent LND, 51 were excluded due to missing data on LN status and survival, therefore 471 patients remained in the final analytic cohort. Median patient age at the time of surgery was 62 years (IQR 53–70) and approximately one-half of patients were male ($n = 220$, 46.7%). The majority of patients were Caucasian ($n = 297$, 66.3%), had an ASA score ≤ 2 ($n = 256$, 54.4%), and did not have cirrhosis ($n = 380$, 80.7%). The preoperative median CA19-9 and CEA were 97 UI/mL (IQR 31–391) and 2.4 ng/mL (IQR 1.4–4.5), respectively; only a minority of patients received neoadjuvant chemotherapy ($n = 57$, 13.6%). Most patients underwent a minor hepatectomy ($n = 387$, 82.7%), whereas a smaller subset underwent a major hepatectomy ($n = 81$, 17.3%). Most patients had unifocal disease ($n = 345$, 78.4%) and the median tumor size was 6.7 cm (IQR 4.5–9.0). Of note, approximately half of the patients

had LNM ($n = 205$, 43.5%). Perhaps not surprisingly, the more common area of LNM was the hepatoduodenal ligament ($n = 373$, 79.7%). The median number of LNs harvested and metastatic LNs was 4 (IQR 2–8) and 0 (IQR 0–1), respectively. The majority of patients had an R0 resection ($n = 379$, 80.5%), MF or IG morphologic ICC type ($n = 334$, 76.3%), and well- to moderate-grade tumors ($n = 342$, 74.2%), whereas the minority had major vascular invasion ($n = 78$, 16.6%). Microvascular invasion was present in 42.2% ($n = 198$) of resected ICCs. Approximately half of the patients received adjuvant chemotherapy ($n = 228$, 51.5%) (Table 1).

Clinicopathological Factors Associated with Lymph Node Dissection, Lymph Node Metastasis, and Cancer-Specific Survival

While the geographical region of treating centers was not associated with the use of LND, patients treated more recently [2013–2016; odds ratio (OR) 2.46, 95% confidence interval (CI) 1.25–4.88], as well as individuals with multifocal disease (OR 2.06, 95% CI 1.59–4.27), tumor > 5 cm (OR 1.73, 95% CI 1.08–2.78), PI or MF + PI morphologic type (OR 20.0, 95% CI 4.15–96.7), and microvascular invasion (OR 1.98, 95% CI 1.14–3.43) were more likely to undergo LND (electronic supplementary Table S2). Among patients with LND, preoperative CEA > 5.0 (OR 2.21, 95% CI 1.20–4.08), PI or MF + PI morphologic type (OR 1.75, 95% CI 1.12–2.72), and major vascular invasion remained associated with LNM (OR 1.76, 95% CI 1.08–2.88) on bivariate analysis (Table 2).

In analyzing CSS, the bivariate analysis revealed several factors that were associated with poorer CSS, including preoperative CA19-9 > 37 [hazard ratio (HR) 1.54, 95% CI 1.06–2.23], preoperative CEA > 5.0 (HR 1.43, 95% CI 1.05–1.96), multifocal disease (HR 1.79, 95% CI 1.31–2.44), tumor size > 5.0 cm (HR 1.43, 95% CI 1.05–1.96), LNM (HR 3.01, 95% CI 2.25–4.01), poor/undifferentiated grade (HR 1.67, 95% CI 1.23–2.26), and major vascular invasion (HR 1.65, 95% CI 1.17–2.34). On multivariable analysis, preoperative CEA > 5.0 (HR 2.65, 95% CI 1.60–4.38), tumor size > 5.0 cm (HR 1.96, 95% CI 1.19–3.21), and LNM (HR 2.74, 95% CI 1.69–4.43) remained associated with CSS (Table 3).

Survival and Therapeutic Index by Perioperative Factors

The median follow-up was 17.9 months (IQR 8.7–36.5). Overall, the frequency of LNM was 43.5%, and 3-year CSS in the entire cohort was 29.9% (Fig. 1a) for a therapeutic index value of 13 (0.435×29.9). Irrespective of other factors, patients with major vascular invasion had the worst

TABLE 1 Demographic and patient characteristics in the entire cohort

Variable	N (%)
Age, years [median (IQR)]	62 (53–70)
Male	220 (46.7)
Race	
Caucasian	297 (66.3)
African American	23 (5.1)
Asian	115 (25.7)
Other	13 (2.9)
ASA score	
≤ 2	256 (54.4)
> 2	215 (45.6)
Cirrhosis	17 (4.3)
CA19-9, UI/mL [median (IQR)]	97 (31–391)
CEA, ng/mL [median (IQR)]	2.4 (1.4–4.5)
Neoadjuvant therapy	
No	362 (86.4)
Yes	57 (13.6)
Type of resection	
Minor	81 (17.3)
Major	387 (82.7)
Location	
Unifocal	345 (78.4)
Multifocal	95 (21.6)
Tumor size, cm [median (IQR)]	6.7 (4.5–9.0)
Lymph node metastasis	
No	266 (56.5)
Yes	205 (43.5)
Lymph node area	
Hepatoduodenal ligament	373 (79.7)
Other station	95 (20.3)
No. of lymph nodes harvested [median (IQR)]	4 (2–8)
No. of lymph nodes harvested	
1–2	147 (33.7)
3–6	148 (33.9)
≥ 7	141 (32.3)
No. of lymph node metastases [median (IQR)]	0 (0–1)
Margin status	
R0	379 (80.5)
R1	92 (19.5)
Morphologic type	
MF, IG	334 (76.3)
PI, MF + PI	104 (23.7)
Grade	
Well to moderate	342 (74.2)
Poor to undifferentiated	119 (25.8)
Major vascular invasion	
No	78 (16.6)
Yes	392 (83.4)

TABLE 1 continued

Variable	N (%)
Microvascular invasion	
No	198 (42.2)
Yes	271 (57.8)
Adjuvant chemotherapy	
No	215 (48.5)
Yes	228 (51.5)

Data are expressed as *n* (%) unless otherwise specified

IQR interquartile range, *ASA* American Society of Anesthesiologists, *CA* carbohydrate antigen, *CEA* carcinoembryonic antigen, *MF* mass-forming, *IG* intraductal growth, *PI* periductal infiltrating

3-year CSS (9.8%), followed by patients with one to two LNs harvested (10.8%), CEA > 5 ng/mL (13.7%), and metastatic LNs in areas other than the hepatoduodenal ligament (15.0%). The highest therapeutic value was noted among patients with seven or more LNs resected (17.8), followed by CEA < 5 ng/mL (16.8), and no major vascular invasion (15). Interestingly, an index difference of more than 10 points was noted only when examining the number of LNs harvested [1–2 (4.1) vs. 3–6 (16.1) vs. ≥ 7 (17.8)]. In turn, patients with three or more LNs harvested had an increased OS compared with patients with one to two LNs resected when the LNs were positive ($p = 0.04$), whereas no survival benefit was noted among patients with non-metastatic LNs ($p = 0.41$) (Fig. 1b, c). Large index differences, although not reaching a value of 10, were also noted for no major vascular invasion [index difference: 9.6; no (15.0) vs. yes (5.4)], CEA ≤ 5 ng/mL [8.4; CEA ≤ 5.0 (16.8) vs. > 5.0 (8.2)], and LNM at the hepatoduodenal ligament [7.3; hepatoduodenal ligament (12.5) vs. other station (5.2)] (Table 4).

DISCUSSION

Lymphadenectomy is an important part of the oncologic resection of ICC as it aids in the adequate staging of the disease, as well as likely decreases locoregional recurrence.^{8,9} Indeed, LND has been suggested to be the standard of care in the treatment of ICC, as reflected in the 8th edition of the American Joint Committee on Cancer (AJCC) staging manual, which suggests at least six LNs be examined to appropriately stage the disease.²³ While resection is the cornerstone of potentially curative therapy for ICC, the prognosis of patients with ICC still remains dismal. In addition, the role of LND has been debated, with clinicians questioning the therapeutic benefit of an LND in the context of ICC treatment. Interestingly, previous nationwide surveys have revealed a relatively low implementation of lymphadenectomy in the surgical treatment of

TABLE 2 Logistic regression analysis of clinicopathological factors associated with lymph node metastasis

Variable	Bivariate analysis		Multivariable analysis	
	OR	95% CI	OR	95% CI
Age, years				
≤ 65	Ref			
> 65	0.78	0.53–1.15		
Sex				
Male	Ref			
Female	0.78	0.54–1.12		
Year				
1990–2008	Ref		Ref	
2009–2012	1.77	1.15–2.73	1.91	0.92–4.00
2013–2016	1.61	1.00–2.59	1.34	0.64–2.82
Hospital				
East	Ref		Ref	
West	0.27	0.17–0.41	0.26	0.15–0.47
CA19-9, UI/mL				
≤ 37	Ref			
> 37	1.40	0.86–2.27		
CEA, ng/mL				
≤ 5.0	Ref		Ref	
> 5.0	2.21	1.20–4.08	1.91	0.96–3.78
Location				
Unifocal	Ref			
Multifocal	1.29	0.82–2.01		
Tumor size, cm				
≤ 5.0	Ref			
> 5.0	0.98	0.66–1.44		
Morphologic type				
MF, IG	Ref		Ref	
PI, MF + PI	1.75	1.12–2.72	1.52	0.74–3.10
Grade				
Well to moderate	Ref			
Poor to undifferentiated	1.08	0.71–1.64		
Major vascular invasion				
No	Ref		Ref	
Yes	1.76	1.08–2.88	1.33	0.61–2.91
Microvascular invasion				
No	Ref			
Yes	1.15	0.79–1.66		

OR odds ratio, CI confidence interval, CA carbohydrate antigen, CEA carcinoembryonic antigen, MF mass-forming, IG intraductal growth, PI periductal infiltrating

ICC, which has not changed over the last decade across the US.^{25,26} The current study was important because we identified a group of patients who seemingly derived the most benefit (so-called ‘therapeutic value’) from LND by utilizing a previously described metric—the therapeutic index.¹⁷ Of note, the highest therapeutic value of LND was

noted among patients with resection of seven or more LNs (17.8), as well as CEA ≤ 5 ng/mL (16.8), tumor size ≤ 5.0 cm (15.6), and no major vascular invasion (15.0). Perhaps of more interest, a therapeutic index interval of more than 10 was noted only among patients having three or more LNs resected, compared with resection of one to

TABLE 3 Cox regression analysis of clinicopathological factors associated with cancer-specific survival

Variable	Bivariate analysis		Multivariable analysis	
	OR	95% CI	OR	95% CI
Age, years				
≤ 65	Ref			
> 65	0.76	0.56–1.04		
Sex				
Male	Ref			
Female	1.30	0.98–1.72		
Year				
1990–2008	Ref			
2009–2012	1.17	0.86–1.59		
2013–2016	0.91	0.55–1.50		
Hospital				
East	Ref		Ref	
West	0.71	0.53–0.96	0.82	0.50–1.34
CA19-9, UI/mL				
≤ 37	Ref		Ref	
> 37	1.54	1.06–2.23	0.91	0.58–1.45
CEA, ng/mL				
≤ 5.0	Ref		Ref	
> 5.0	2.81	1.85–4.28	2.65	1.60–4.38
Neoadjuvant therapy				
No	Ref			
Yes	1.12	0.72–1.74		
Location				
Unifocal	Ref		Ref	
Multifocal	1.79	1.31–2.44	1.31	0.75–2.29
Tumor size, cm				
≤ 5.0	Ref		Ref	
> 5.0	1.43	1.05–1.96	1.96	1.19–3.21
Type of resection				
Minor resection	Ref			
Major resection	1.09	0.76–1.57		
Lymph node metastasis				
No	Ref		Ref	
Yes	3.01	2.25–4.01	2.74	1.69–4.43
Margin status				
R0	Ref			
R1	1.24	0.87–1.78		
Morphologic type				
MF, IG	Ref			
PI, MF + PI	1.34	0.98–1.84		
Grade				
Well to moderate	Ref		Ref	
Poor to undifferentiated	1.67	1.23–2.26	1.20	0.70–2.06
Major vascular invasion				
No	Ref		Ref	
Yes	1.65	1.17–2.34	1.44	0.84–2.47

TABLE 3 continued

Variable	Bivariate analysis		Multivariable analysis	
	OR	95% CI	OR	95% CI
Microvascular invasion				
No	Ref			
Yes	1.00	0.75–1.33		
Adjuvant chemotherapy				
No	Ref			
Yes	1.07	0.80–1.44		

OR odds ratio, CI confidence interval, CA carbohydrate antigen, CEA carcinoembryonic antigen, MF mass-forming, IG intraductal growth, PI periductal infiltrating

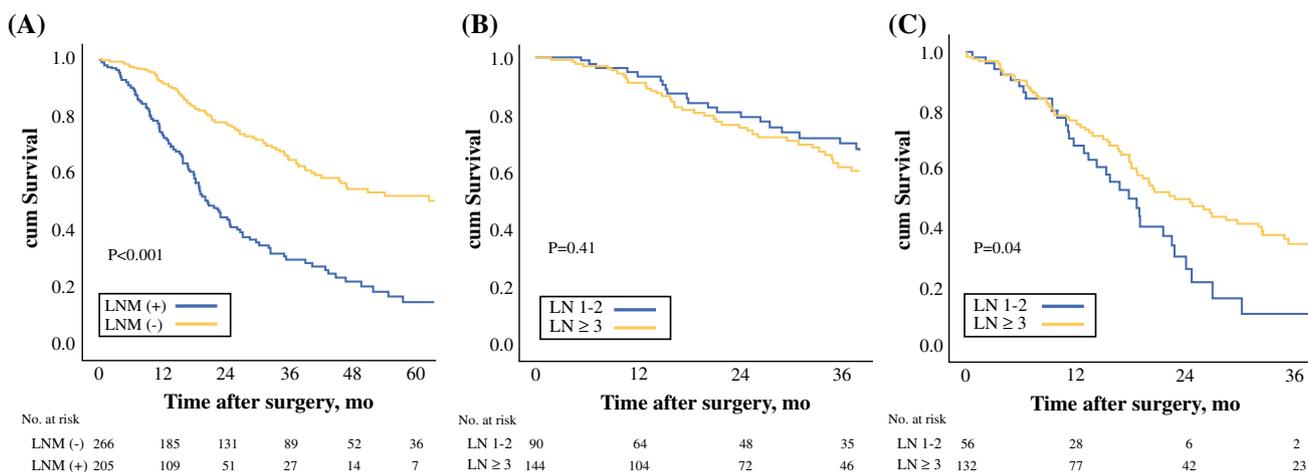


FIG. 1 Kaplan–Meier curves showing cancer-specific survival among patients with LND in total (a), and among patients without (b) and with LNM (c), stratified by the number of LNs harvested. LND lymph node dissection, LNM lymph node metastasis, LNs lymph nodes, Cum cumulative

two LNs [1–2 (4.1) vs. 3–6 (16.1) vs. ≥ 7 (17.8)]. In addition, a better prognosis was noted among patients with LNM and three or more LNs harvested. In contrast, the lowest therapeutic value of LND was noted among patients with major vascular invasion (index 5.4), one to two LNs resected (4.1), and LN metastases at stations other than the hepatoduodenal ligament (5.2). To the best of our knowledge, this is the first study to utilize the therapeutic index to evaluate the therapeutic benefit associated with LND among patients treated for ICC.

The therapeutic index was first proposed by Sasako et al. in an attempt to evaluate the role of LND in the treatment of gastric cancer.¹⁷ The therapeutic index metric calculates the therapeutic efficacy of LND among patients with certain characteristics, or LND in certain stations, without taking other nodal status into account, thus avoiding stage migration.¹⁷ The rationale of the therapeutic index, which is calculated easily using frequency of LNM and long-term

survival among patients having LNM, is that LND should ideally be performed among patients with a higher predicted incidence of LNM who could derive a benefit from LND.¹⁷ Indeed, the optimal number of LNs harvested should be assessed not only on the basis of precise staging related to patients without LNM but also as a means of eliminating locoregional disease among patients with LNM. Given the debated role of LND in the treatment of patients with ICC,²⁰ we sought to apply this metric in the evaluation of the therapeutic value of LND among patients undergoing surgery for ICC. Of note, the data demonstrated that resection of three to six LNs and seven or more LNs was associated with a considerable therapeutic index compared with patients who had one or two harvested LNs (with the difference being more than 10), which was in line with the 8th edition of the AJCC staging manual, which recommends six or more LNs be evaluated to stage ICC properly.²³

TABLE 4 Therapeutic index stratified by clinicopathological factors

Variable	Frequency of LNM	3-year CSS (%)	Therapeutic index
Overall	0.435 (205/471)	29.9	13.0
CA19-9, UI/mL			
≤ 37	0.406 (39/96)	35.8	14.5
> 37	0.489 (110/225)	30.4	14.9
CEA, ng/mL			
≤ 5.0	0.404 (76/188)	41.7	16.8
> 5.0	0.600 (33/55)	13.7	8.2
Location			
Unifocal	0.418 (152/364)	32.9	13.8
Multifocal	0.480 (47/98)	21.2	10.2
Tumor size, cm			
≤ 5.0	0.438 (67/153)	35.7	15.6
> 5.0	0.432 (136/315)	27.8	12.0
Morphologic type			
MF, IG	0.419 (140/334)	32.9	13.8
PI, MF + PI	0.558 (58/104)	25.3	14.1
Grade			
Well to moderate	0.436 (149/342)	32.7	14.3
Poor to undifferentiated	0.454 (54/119)	22.6	10.3
Major vascular invasion			
No	0.411 (161/392)	36.4	15.0
Yes	0.551 (43/78)	9.8	5.4
Lymph node area			
Hepatoduodenal ligament	0.386 (173/448)	32.3	12.5
Other station	0.347 (33/95)	15.0	5.2
No. of LNs harvested			
1–2	0.381 (56/147)	10.8	4.1
3–6	0.466 (69/148)	34.5	16.1
≥ 7	0.504 (71/141)	35.3	17.8

LNM lymph node metastasis, CSS cancer-specific survival, CA carbohydrate antigen, CEA carcinoembryonic antigen, MF mass-forming, IG intraductal growth, PI periductal infiltrating, LNs lymph nodes

Previous studies have demonstrated no improvement in survival or recurrence associated with routine lymphadenectomy.^{7,9,27–30} In particular, Hu et al. reported that routine lymphadenectomy may not improve long-term survival among patients with resectable ICC and no evidence of LNM preoperatively.²⁷ Of note, lymphadenectomy may even be associated with an increased risk of complications in certain subsets of patients. For example, among patients with cirrhosis, the incidence of complications was 71% among patients who underwent a lymphadenectomy versus 23% among patients who did not.³¹ To this end, surgeons need to weigh the risks and potential benefit derived by lymphadenectomy for each patient. In the current study, the survival benefit reflected by the therapeutic index was lower among patients with major vascular invasion (5.4), preoperative

CEA > 5.0 (8.2), and LNM in stations other than hepatoduodenal ligament (5.2), suggesting that these factors may indicate systemic spread rather than locally advanced disease, and thus lymphadenectomy may not be as beneficial to help stage patients or provide a therapeutic benefit. In fact, lymphadenectomy beyond the hepatoduodenal ligament, including the common hepatic artery basin, is unlikely to improve outcomes, even if macroscopic radical LND can be achieved.³² Therefore, the adoption of routine lymphadenectomy for patients with major vascular invasion, preoperative CEA > 5.0, or LNM in extended areas may not be warranted. In contrast, patients who do not have these features should be strongly considered for LND as the therapeutic index associated with this procedure suggests a benefit for this subset of individuals. Hence, future

prospective studies are needed to verify the therapeutic value of LND among select patients with and without the unfavorable prognostic factors.

While one strength of the current study was that it involved multiple centers, the multi-institutional nature of the study may have possibly introduced certain biases (i.e. selection bias of patients who were offered surgery and lymphadenectomy, missing information on variables of interest, such as CEA, CA19-9 levels, variability in treatment methods, and follow-up schemas among institutions). It was also not possible to standardize the cut-off value of the therapeutic index relative to lymphadenectomy for a certain subgroup; however, using the index, we were able to compare subgroups in regard to the relative therapeutic value of lymphadenectomy.²⁰ In addition, analysis of the therapeutic value of LND by ICC 'sidedness' was not feasible in the current study. Finally, information on adjuvant therapy and its potential impact on survival was not included in the analysis of the therapeutic index. Even though data from the BILCAP study have suggested that adjuvant capecitabine improved survival after resection of biliary tract cancers,³³ the PRODIGE study recently noted that adjuvant gemcitabine and oxaliplatin (GEMOX) did not confer a survival benefit despite an acceptable safety/tolerance profile.³⁴ The reasons for these disparate results are unclear, but may relate to the fact that there were more patients with LN metastasis and an R1 resection margin in the BILCAP study versus the PRODIGE trial. In turn, this may suggest that adjuvant therapy has a more beneficial effect among patients who have adverse prognostic factors (i.e. LN metastasis and R1 margins) relative to those individuals who do not.

CONCLUSION

The survival benefit derived from lymphadenectomy was poor among patients with major vascular invasion, CEA > 5.0 ng/mL, and LNM in areas other than the hepatoduodenal ligament. Resection of three or more LNs was associated with the highest therapeutic value among patients with LNM.

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