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ORIGINAL ARTICLE

The impact of tumor location on the value of lymphadenectomy for intrahepatic cholangiocarcinoma

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Abstract

Background: The therapeutic role of lymphadenectomy (LND) for intrahepatic cholangiocarcinoma (ICC) patients remains ill-defined. We sought to analyze the therapeutic value of LND relative to tumor location and preoperative lymph node metastasis (LNM) risk.

Methods: Patients who underwent curative-intent hepatic resection of ICC between 1990 and 2020 were included from a multi-institutional database. Therapeutic LND (tLND) was defined as LND that harvested $\geq$3 lymph nodes.

Results: Among 662 patients, 178 (26.9%) individuals received tLND. Patients were categorized into central type ICC (n = 156, 23.6%) and peripheral type ICC (n = 506, 76.4%). Central type harbored multiple adverse clinicopathologic factors and worse overall survival (OS) compared with peripheral type (5-year OS, central: 27.0% vs. peripheral: 47.2%, $p < 0.001$). After consideration of preoperative LNM risk, patients with central type and high-risk LNM who underwent tLND survived longer than individuals who did not (5-year OS, tLND: 27.9% vs. non-tLND: 9.0%, $p = 0.001$), whereas tLND was not associated with better survival among patients with peripheral type ICC or low-risk LNM. The therapeutic index of hepatoduodenal ligament (HDL) and other regions was higher in central type than in peripheral type, which was more pronounced among high-risk LNM patients.

Conclusions: Central type ICC with high-risk LNM should undergo LND involving regions beyond the HDL.

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Introduction

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver cancer, representing approximately 10–20% of all primary liver tumors.[1] The worldwide incidence of ICC has been rising over the last several decades in both Eastern and Western countries.[2] Liver resection remains the mainstay of curative treatment, although long-term outcomes remain poor in some circumstances.[3] Notably, lymph node metastasis (LNM) is an established, independent determinant of poor long-term outcomes among patients with ICC patients.[4,5] Given the high incidence of LNM, which can range from 20 to

60%,[6,7] lymphadenectomy (LND) has been recommended for adequate staging and local disease control.[8] As such, some surgeons have advocated for combined resection and LND as the optimal oncologic approach to ICC.[9]

There have been, however, conflicting results regarding the extent of LND and its potential therapeutic role.[10–13] Although several investigators have promoted routine LND for all ICC patients to ensure accurate staging, only a few studies have investigated the potential benefits of performing LND concomitant with resection of ICC.[10,11] In turn, due to the scarcity of evidence regarding any therapeutic benefit of LND, several authors have argued that routine LND is unnecessary in the setting of ICC patients.[12,13] Proponents of LND have noted, however, that assessment of the nodal basin is critical to stage patients accurately, may inform adjuvant therapy, and could possibly have a therapeutic benefit in specific subpopulations of patients with ICC.[14,15] In particular, LND that includes the evaluation of $\geq$3 lymph nodes may be associated with a therapeutic benefit among patients with nodal disease.[14] In addition to the number of nodes, other authors have suggested that the benefit of LND in the setting of ICC may be impacted by anatomic location. For example, Umeda et al. reported that individuals with ICC involving the hepatic hilum who underwent adequate LND achieved more favorable long-term outcomes.[15] Therefore, LN number, status, and primary tumor location may all impact the relative benefit of LND.

The enhanced imaging score (EIS) has utilized preoperative characteristics of the primary ICC tumor in an attempt to predict lymph node metastases, and thus identify patients who may derive the greatest survival benefit from LND.[16] In particular, ICC can be defined anatomically based on peripheral versus central location.[17] Little is known, however, about the interplay between tumor location and the therapeutic value of LND, as well as the optimal extent of LND required to achieve maximum therapeutic benefit. Therefore, the objective of the current study was to characterize the clinicopathologic differences in ICC relative to tumor location, as well as the differential impact of LND on long-term survival relative to tumor location. In particular, the optimal extent of LND with regards to tumor location and EIS was examined using the therapeutic index, a concept of measuring LND at a specific basin.[14,18]

Methods

Data source and patient selection

Patients who underwent curative-intent hepatectomy for ICC between 1990 and 2020 were identified from the International Intrahepatic Cholangiocarcinoma Study Group database, which is comprised of 16 high-volume hepatobiliary hospitals worldwide.[5–7,14] Patients who underwent palliative surgery or R2 resection, had missing information on lymphadenectomy, laboratory or pathological findings, and had no follow-up data were excluded. The Institutional Review Boards of all the participating institutions approved this study.

Variables and outcomes

Demographic and clinicopathologic data were evaluated including age, gender, American Society of Anesthesiologist (ASA) classification, cirrhosis, preoperative carbohydrate antigen (CA) 19-9 levels (IU/mL), albumin-bilirubin (ALBI) grade (i.e. grade1, grade 2/3), preoperative lymph node status (i.e. negative, suspicious/positive) and EIS. Furthermore, data on tumor size (cm) and number, tumor burden score (TBS), extent of resection, therapeutic lymphadenectomy (tLND), bile duct resection, T-category based on AJCC 8th edition,[19] nodal disease (i.e. N0: negative; Nx: not examined; N1: positive), location of lymphadenectomy, margin status (i.e. R0, R1), tumor histological grade, morphological subtype, microvascular invasion, major vascular invasion, tumor location (i.e. peripheral, central), and receipt of adjuvant chemotherapy were collected. Central type ICC was defined as an intrahepatic tumor, the center of which was away from the hepatic hilum (i.e. the area between the left side of the right posterior portal vein and the right side of the umbilical portion of the left portal vein), yet with no direct involvement of the hilar region and/or preoperative jaundice due to tumor compression. In contrast, peripheral type ICC was defined as a tumor with none of the above characteristics.[20] The extent of LND was classified into two categories: hepatoduodenal ligament (HDL), and other basins (including common hepatic artery, post-pancreatic head, celiac, and para-aortic lymph nodes).[5,14] A therapeutic LND (tLND) was achieved when more than three nodes were harvested.[14,21] Margin status was defined as microscopically negative (>0 mm, R0) or microscopically positive (R1); margin width was classified as R1, 0–3 mm, 3–10 mm, and >10 mm.[22] TBS, a concise metric of ICC tumor burden, was calculated based on the formula [TBS^2 = (maximum tumor diameter)^2 + (number of tumors)^2].[23] EIS as a preoperative lymph node metastases risk score was calculated according to the following formula: 1.23−0.016 × Age + 0.146 × Number of lesions + (if lymph nodes on imaging suspicious or positive, 1.143) + (if CA19-9 > 200 IU/mL, 0.514) + (if ALBI grade 2/3, 0.345), as previously validated (available online: https://k-sahara.shinyapps.io/ICC_imaging/).[16] Patients with an EIS of 0.886 or more were considered at high risk of LNM, as previously defined.[16] The severity of surgical complications was defined according to the Clavien-Dindo-classification. The primary outcome was overall survival (OS), defined as the time interval between the dates of resection to the date of death from any cause or last follow-up.

Therapeutic index

The therapeutic index was estimated for both clinicopathological and lymph node-related characteristics with regard to the extent of LND. The therapeutic index of LND was calculated by multiplying the frequency of LNM in a particular group of patients by the 5-year cancer-specific survival (CSS) rate of patients with LNM in that group, as previously reported.[24,25] The incidence of LNM was calculated by dividing the number of patients

with nodal disease by the total number of patients who underwent LND in a specific area (i.e. HDL or other areas). Patients who were alive or had died of other causes than ICC were censored when analyzing CSS. The 5-year CSS was calculated for each group of patients with metastatic lymph nodes, regardless of the number of lymph nodes examined. In cases in which the difference in therapeutic index values were more than 10, LND was considered meaningful.[14,24]

Statistical analysis

Descriptive statistics were presented as medians [interquartile ranges (IQRs)] for continuous variables and frequency (%) for categorical variables. All tests were 2-sided, and a p-value <0.05 was considered statistically significant. Continuous variables were compared with the Mann–Whitney *U* test, and categorical variables using the chi-square test, or Fisher exact test, as appropriate. Survival probabilities were estimated using the Kaplan–Meier curve and compared using the log-rank test. Multivariable analysis was performed using Cox proportional hazard model using the backward-elimination approach. All statistical analyses were performed using SPSS software version 28.0 (IBM Corporation, Armonk, NY) and R version 4.2.0 (R Project for Statistical Computing, Vienna, Austria).

Results

Patient demographics: peripheral and central type ICC

Among 662 patients who met inclusion criteria, median age was 57.1 years (IQR, 49.0–66.0) and 404 (61.0%) patients were male (Table 1). Approximately one-fourth of patients had CA19-9 >200 IU/mL (n = 165, 25.5%) and ALBI grades 2 or 3 (n = 194, 29.3%), whereas roughly 1 in 5 patients (n = 124, 18.7%) had preoperatively suspicious/metastatic lymph nodes. Overall, 178 (26.9%) patients underwent tLND. On final pathology, only a small subset of patients (n = 76, 11.6%) had multiple lesions and median tumor size was 5.7 cm (IQR, 4.0–8.0) corresponding to a median TBS of 5.9 (IQR, 4.1–8.1). A minority of patients presented with T2/3/4 ICC (n = 257, 38.8%) or had metastatic nodal disease (n = 133, 20.1%). In addition, a subset of patients had microvascular invasion (n = 184, 27.8%), major vascular invasion (n = 86, 13.0%), periductal infiltrating morphological subtype (n = 75, 11.3%), poorly or undifferentiated tumors (n = 96, 14.5%), or an R1 resection (n = 66, 10.0%).

More than three-quarters of patients had peripheral type ICC (n = 506, 76.4%), while a minority had central type ICC (n = 156, 23.6%). Patients with central type ICC were less likely to present with cirrhosis (central: n = 144, 93.3%; peripheral: n = 431, 85.2%) versus peripheral type ICC; however, patients with central type ICC were older (central: 62.0 [52.0–72.8] vs. peripheral: 57.0 [48.0–65.0]), more likely to present with preoperative suspicious LNM (central: n = 48, 43.3%; peripheral: n = 75, 14.8%), as well as have a higher likelihood of CA19-9>200 IU/mL (central: n = 60, 33.7%; peripheral: n = 109, 21.5%) and ALBI grade 2/3 (central: n = 77, 43.3%; peripheral: n = 117, 23.1%) (all p < 0.001). In turn, patients with central type ICC were more likely to be classified as EIS high-risk than patients with peripheral type ICC (central: n = 91, 58.3% vs. peripheral: n = 117, 35.0%) (p < 0.001). Furthermore, patients with central type ICC more frequently underwent major resection (central: n = 130, 73.0%; peripheral: n = 210, 41.5%), tLND (central: n = 92, 51.7%; peripheral: n = 86, 17.0%), and bile duct resection (central: n = 89, 57.1%; peripheral: n = 34, 6.7%) (all p < 0.001). Tumor location was also associated with a number of adverse clinicopathologic features including advanced AJCC T- and N-categories (T2/3/4, central: n = 118, 75.6%; peripheral: n = 139, 27.4%; N1, central: n = 67, 42.9%; peripheral: n = 66, 13.0%), microvascular invasion (central: n = 91, 58.3%; peripheral: n = 93, 18.4%), major vascular invasion (central: n = 70, 44.9%; peripheral: n = 16, 3.2%), poor tumor differentiation (central: n = 37, 23.7%; peripheral: n = 59, 11.7%), periductal infiltrating subtype (central: n = 53, 34.0%; peripheral: n = 22, 4.3%), an R1 resection (central: n = 32, 20.5%; peripheral: n = 34, 6.7%) (all p < 0.001). Additionally, patients with peripheral type ICC were more likely to have a wider margin width versus individuals with central type ICC (Table 1).

Survival: the impact of tLND on patients with peripheral and central type ICC

With a median follow-up of 22.3 months (IQR 11.2–42.2 months), 5-year OS was 42.1% in the overall cohort. Patients with central type ICC had worse 5-year OS than individuals with peripheral type ICC (5-year OS, 27.0% vs. 47.2%, p < 0.001) (Fig. 1). The tLND and non-tLND groups had comparable 5-year OS in peripheral type ICC (tLND: 36.0% vs. non-tLND: 49.0%, p = 0.32), as well as central type ICC (tLND: 26.6% vs. non-tLND: 21.5%, p = 0.14) (Supplementary Fig. 1). On multivariable Cox regression analysis, tLND was not a predictor of survival among patients with either peripheral or central type ICC (Supplementary Table 1). To evaluate further the impact of tLND, the probability of LNM was taken into account using EIS. Considering preoperative LMN risk, central type ICC patients at high-risk of LNM had a survival benefit from tLND compared with non-tLND (tLND: 27.9% vs. non-tLND: 9.0%, p = 0.001). In contrast, there was no survival difference associated with tLND among patients with central type ICC at high-risk of LNM and peripheral type ICC regardless of LNM risk (central type at low-risk LNM, tLND: 41.9% vs. non-tLND: 29.4%, p = 0.19; peripheral type at low-risk LNM, tLND: 11.1% vs. non-tLND: 26.7%, p = 0.91; peripheral type at high-risk LNM, tLND: 59.4% vs. non-tLND: 59.3%, p = 0.86) (Fig. 2). Similar results were obtained on multiple regression analysis. Specifically, tLND was an indepedent predictor of OS among patients with central type ICC at high risk of LNM (hazard ratio [HR] 0.53, 95%CI 0.28–0.94, p = 0.04), as well as patients with positive surgical resection margins (HR 2.17, 95%CI 1.13–4.91, p = 0.02); in

Table 1 Baseline characteristics of patients

Characteristics	Total (n = 662)	Peripheral (n = 506, 76.4%)	Central (n = 156, 23.6%)	P-value
Demographic				
Age, y, median (IQR)	57.1 (49.0–66.0)	57.0 (48.0–65.0)	62.0 (52.0–72.8)	**<0.001**
Sex, male, n (%)	404 (61.0)	309 (61.1)	95 (60.9)	0.95
ASA PS classification, >II, n (%)	167 (25.2)	124 (24.5)	43 (24.2)	0.43
Cirrhosis, n (%)	84 (13.1)	75 (14.8)	12 (6.7)	**0.02**
Preoperative data				
CA19-9, 200U/mL, n (%)	169 (25.5)	109 (21.5)	60 (33.7)	**<0.001**
ALBI grade, 2/3, n (%)	194 (29.3)	117 (23.1)	77 (43.3)	**<0.001**
Preoperative lymph node, suspicious/positive, n (%)	124 (18.7)	75 (14.8)	49 (27.5)	**<0.001**
Enhanced imaging score, high-risk, n (%)	208 (40.5)	117 (35.0)	91 (58.3)	**<0.001**
Perioperative data				
Extent of liver resection, Major, n (%)	340 (51.4)	210 (41.5)	130 (73.0)	**<0.001**
Therapeutic lymphadenectomy, n (%)	178 (26.9)	86 (17.0)	92 (51.7)	**<0.001**
Bile duct resection, n (%)	172 (26.0)	34 (6.7)	89 (57.1)	**<0.001**
Adjuvant chemotherapy, n (%)	123 (18.6)	98 (19.4)	74 (47.4)	**<0.001**
Pathologic data				
Tumor number, median (IQR)	1 (1–1)	1 (1–1)	1 (1–1)	0.95
The largest tumor size, cm, median (IQR)	5.7 (4.0–8.0)	6.0 (4.0–8.0)	5.4 (3.6–8.0)	0.16
Tumor burden score, median (IQR)	5.9 (4.1–8.1)	6.1 (4.1–8.1)	5.5 (3.7–8.1)	0.23
AJCC T-category, n (%)				
T1a/T1b	405 (61.2)	367 (72.5)	38 (24.3)	**<0.001**
T2/3/4	257 (38.8)	139 (27.4)	118 (75.6)	
Lymph node metastases, n (%)				
N0	185 (27.9)	124 (24.5)	61 (39.1)	**<0.001**
Nx	344 (52.0)	316 (62.4)	28 (17.9)	
N1	133 (20.1)	66 (13.0)	67 (42.9)	
Microvascular invasion, n (%)	184 (27.8)	93 (18.4)	91 (58.3)	**<0.001**
Major vascular invasion, n (%)	86 (13.0)	16 (3.2)	70 (44.9)	**<0.001**
Morphologic type, PI/MF + PI, n (%)	75 (11.3)	22 (4.3)	53 (34.0)	**<0.001**
Grade, poor/undifferentiated, n (%)	96 (14.5)	59 (11.7)	37 (23.7)	**<0.001**
R1 resection, n (%)	66 (10.0)	34 (6.8)	32 (20.5)	**<0.001**
Margin width, n (%)				
R1	66 (10.5)	34 (6.8)	32 (20.5)	**<0.001**
0–3 mm	203 (32.4)	161 (32.0)	74 (47.4)	
3-10 mm	239 (38.1)	204 (40.6)	35 (22.4)	
≥10 mm	119 (19.0)	104 (20.7)	15 (9.6)	

ASA PS, American Society of Anesthesiologists Physical Status; ALBI grade, albumin-bilirubin grade; AJCC, American Joint Committee of Cancer 8th edition; PI/MF + PI, periductal infiltrating/mass forming plus periductal infiltrating.
R1 resection was defined as microscopically positive.

contrast, tLND was not associated with OS among the other groups (Table 2).

Among the entire cohort and, in particular, among patients with peripheral type ICC, tLND was associated with a higher incidence of postoperative complications, severe postoperative complications, and readmittion within 30 days. In contrast, there were no differences in short-term outcomes among tLND and non-tLND patients with central type ICC (Supplementary Table 2).

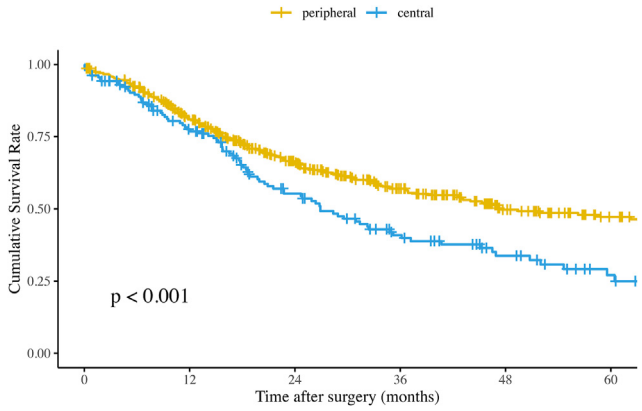

Figure 1 Overall survival of patients according to tumor location

The therapeutic index relative to different lymph node basins

The therapeutic benefit of LND in HDL or other nodal basins was assessed using the therapeutic index. Table 3 summarizes therapeutic indices of LND stratified by LN basins among all patients, as well as among only patients deemed to be preoper-

Table 2 Multivariable analysis of overall survival with stratification of tumor location and preoperative lymph node metastasis risk

Characteristics	Multivariable		
	HR	95%CI	p-value
(A) LNM low-risk peripheral ICC			
Tumor burden score	1.06	1.00–1.12	**0.04**
(B) LNM low-risk central ICC			
Tumor burden score	1.09	1.04–1.14	**<0.001**
(C) LNM high-risk peripheral ICC			
CA19-9, >200 U/mL	2.15	1.43–3.21	**<0.001**
Lymph node metastases			
N0	Ref		
Nx	1.68	0.96–2.91	0.07
N1	2.12	1.15–3.91	**0.02**
(D) LNM high-risk central ICC			
Therapeutic lymphadenectomy	0.53	0.28–0.94	**0.04**
R1 resection	2.17	1.13–4.19	**0.02**

LNM, lymph node metastasis; ICC, intrahepatic cholangiocarcinoma; R1, resection was defined as microscopically positive.

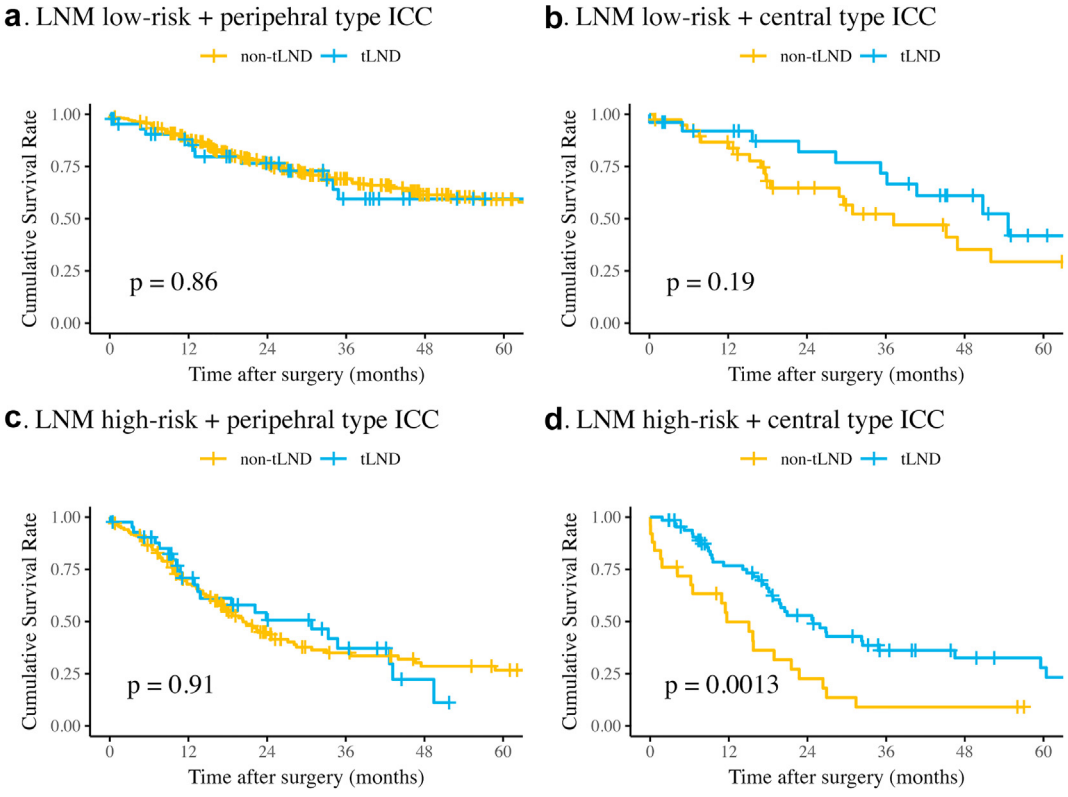

Figure 2 Overall survival of patients with and without therapeutic lymphadenectomy according to tumor location with stratification according to lymph node metastasis (LNM) risk. tLND; therapeutic lymphadenectomy

Table 3 Therapeutic indices by the lymphadenectomy of specific areas in all patients and preoperative lymph node metastasis high-risk patients

	Lymph node Area	Incidence of nodal disease in each lymph node area	Cancer Specific 5-year survival rate (%, 95%CI)	Therapeutic index
Peripheral	Hepatoduodenal ligament	0.35	15.3 (1.4–43.5)	5.3 (0.5–15.1)
	Other areas	0.50	0	0
Central	Hepatoduodenal ligament	0.53	27.2 (13.9–42.4)	14.5 (7.4–22.6)
	Other areas	0.63	30.1 (9.6–54.2)	19.0 (6.0–34.1)
Peripheral with LNM high-risk	Hepatoduodenal ligament	0.56	0	0
	Other areas	0.55	0	0
Central with LNM high-risk	Hepatoduodenal ligament	0.65	27.3 (13.3–43.4)	17.9 (8.7–28.4)
	Other areas	0.62	16.8 (2.7–41.5)	10.4 (1.7–25.7)

LNM, lymph node metastases.

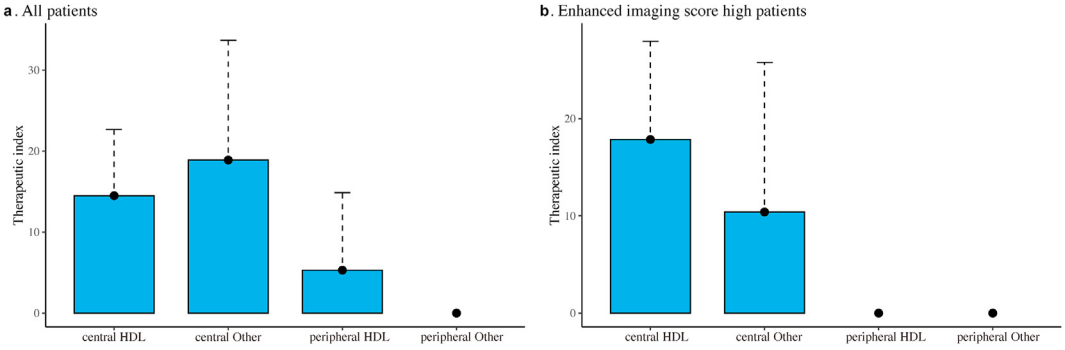

Figure 3 Therapeutic index of lymph nodes in the hepatoduodenal ligament and other sites in the preoperative LMN high-risk group. The therapeutic index was calculated by multiplying the frequency of lymph node metastases by the 5-year cancer-specific survival of patients with lymph node metastases in that group (%, 95%CI). Dotted line showed upper 95%CI of therapeutic index. HDL, hepatoduodenal ligament

atively at high-risk for LNM. Among patients with peripheral type ICC, the therapeutic index was calculated to be 5.3 points (95%CI 0.5–15.1) in HDL and 0 points in other areas; in contrast, it was calculated to be 14.5 points (95%CI 7.4–22.6) in HDL and 19.0 points (95%CI 6.0–34.1) in central type ICC. Of note, the therapeutic index of central type ICC patients at high-risk of LNM was 17.9 (95%CI 8.7–28.4) in HDL and 10.4 (95% CI 1.7–25.7) in other areas. In contrast, the therapeutic index of patients with peripheral ICC at high-risk of LNM was 0 points regardless of lymph node basins, resulting in a greater than 10-point difference between central and peripheral type ICC in both lymph node basins (Fig. 3).

Discussion

Although the AJCC 8th edition staging manual and expert consensus advocate for routine LND as the standard of care, the therapeutic benefit of LND for ICC patients remains ill-defined.[8,9,19] Prior studies have reported inconsistent results regarding subgroups that might achieve a better outcome with LND, along with the optimal extent of LND.[5,26,27] The discrepancy in previous data may derive from the heterogeneity in patient and disease characteristics. As such, the therapeutic value of LND and the extent of LND should be assessed taking into account various tumor characteristics, including primary tumor location.[14] The current study was important because it demonstrated the differential survival benefit of LND relative to tumor location and preoperative risk of LNM. Of note, the current study demonstrated that patients with central type ICC had a worse 5-year OS versus individuals with peripheral type. Although a survival benefit was achieved with tLND among patients with central type ICC who were preoperatively at high-risk of LNM, patients with peripheral type ICC or central type ICC who were at low-risk of LNM preoperatively did not experience a survival benefit from tLND. In addition, tumor location and preoperative LNM risk affected the therapeutic index of lymph node basins. Specifically, patients with central type ICC and were at preoperative high-risk for LNM had a therapeutic index of 17.9 (8.7–28.4) in HDL and 10.4 (1.7–25.7) in HDL and other LN areas, respectively. In contrast, the therapeutic index among patients with peripheral ICC who were high-risk of LNM preoperatively was 0 points regardless of

lymph node basins, resulting in a greater than 10-points difference between central and peripheral type ICC in both lymph node basin areas.

Traditionally, ICC has been anatomically subclassified into two groups relative to the origins of bile ducts: intrahepatic tumors involving the main bile duct or the intrahepatic second or third branches (i.e. hilar or central type) versus tumors involving the small, segmental branches (i.e. peripheral type).[17] Several reports have demonstrated distinct clinicopathologic differences between these two ICC subtypes; specifically, patients with ICC involving hilar regions have a higher probability of lymphatic invasion and periductal infiltration, resulting in more extensive disease and subsequently worse survival.[20,28–30] In line with these findings, the current study noted that central type ICC was associated with a higher likelihood of adverse clinicopathologic determinants (i.e., nodal disease, central: 37.6% vs. peripheral: 13.0%; periductal infiltrating subtype, central: 29.8% vs. peripheral: 4.3%; both $p < 0.001$), as well as a narrower margin width versus peripheral type ICC. Furthermore, patients with central type ICC were more likely to have a worse prognosis versus individuals with peripheral type ICC – likely based on differences in baseline unfavorable tumor characteristics (Fig. 1). In addition, patients with central type ICC who underwent adjuvant therapy had a more favorable survival profile (HR 0.62, 95%CI 0.41–0.95, $p = 0.03$); in contrast, adjuvant therapy was not associated with improved survival among patients with peripheral type ICC (Supplementary Table 1). In turn, adjuvant therapy may benefit only that subset of patients who have ICC with more adverse clinicopathological characteristics.[31,32] Interestingly, molecular-based analysis has revealed differences among cholangiocarcinoma lesions located in various parts of the bile ducts, suggesting that molecular biology dictates tumor behavior.[17,33] The variation of aberrant gene expression or oncogenic pathways may therefore influence the distinctive features among central and peripheral type ICCs. Collectively, understanding variations in the origin of ICC may hold the key to developing therapeutic strategies that confer maximal survival benefit.

Although previous studies failed to demonstrate an advantage in long-term prognosis associated with routine LND for the overall ICC population, specific sub-populations of patients with ICC may benefit from LND.[10,26] Previous studies had demonstrated conflicting results relative to which patients may benefit from LND, as well as the optimal number of lymph node that should be harvested. For example, some researchers demonstrated that LND $\geq$3 lymph nodes, which was adopted by the current study, was associated with improved outcomes,[14] whereas in a different study the authors noted that harvesting $\geq$6 lymph nodes led to better outcomes and more accurate staging.[34] Of note, in the current study, tLND (LND$\geq$3) was associated with better long-term survival among patients with central type ICC who were deemed high-risk preoperatively for LNM, without an increased incidence of worse short-term outcomes (Fig. 2, Table 2, and Supplementary Table 2). This finding was consistent with previous studies that suggested LND contributed to improved survival for patients with tumors occupying the hilar region of the liver.[15,35,36] In the present study, preoperative LNM risk had an impact on the therapeutic value of tLND. Since the removal of clinically suspicious nodal disease is crucial to achieve complete resection of diseased sites, preoperative assessment of LMN is important to inform the treatment strategy. Taken together, tLND was most beneficial among patients with a greater risk of LMN; in turn, LND should be particularly considered for patients with central type ICC who have a high preoperative risk of LNM. In contrast, LND may not be as benefical among patients with peripheral type ICC or individuals deemed to be low-risk preoperatively for LNM or with cirrhosis, as the survival benefit of LND was diminished and the yield of LND to stage patients may be lower.

The extent of LND at the time of surgery for ICC has been a topic of debate. The AJCC 8th manual recommends that regional LND should include the HDL and gastrohepatic lymph nodes for left-sided ICC and the HDL and peripancreatic lymph nodes for right-sided ICC, although the meaning of LND beyond regional lymph node basins has been unclear.[19] The therapeutic index was first proposed to evaluate LND among patients being treated for gastric cancer.[24,37] Since then, the therapeutic index metric has been applied to various other cancers and lymph node basins including rectal cancer (pelvic lymph nodes) and lung cancer (mediastinal lymph nodes).[25,38] Given the increasing adoption of the therapeutic index with other cancers, we believe that the current study is important to demonstrate its potential role for patients with ICC.[14,18] Using the therapeutic index, it is possible to assess not only the staging ability, but also the benefits of local control from the removal of specific lymph nodes. In the current study, the therapeutic index of central type ICC was high in the HDL and other lymph node basins compared with peripheral type ICC. The therapeutic benefit was particularly pronounced among patients who were at high-risk preoperatively for LNM, resulting in a meaningful difference between the two groups (HDL: central type with LNM high-risk, 17.9 vs. peripheral type with LNM high-risk, 0; other basins: central type with LNM high-risk, 10.4 vs. peripheral type with LNM high-risk, 0) (Fig. 3 and Table 3). These data suggested that LND involving regional plus other nodal basins (including common hepatic artery, peripancreatic) need to be dissected at the time of sugery for central type ICC, especially among patients with high-risk of LNM; in contrast, lymph node basins beyond HDL are unlikely to be necessary among patients with peripheral type ICC. Collectively, data from the current study, as well as other previous reports,[5,11,39] strongly suggest that LND including HDL and other basins may lead to better prognostication and more favorable survival depending on tumor location and preoperative LNM risk.

There were several limitations that should be taken into account when interpreting the results of the current study. Due to

the rarity of ICC, a large international multi-institutional database that contained patients from multiple decades was necessary to ensure a sufficient sample size. Although the multicenter nature of the study was a strength, treatment approaches (i.e., the indication of LND) among institutions over time may have varied. Of note, the utilization of LND was relatively low in the current study, consistent with previous data demonstrating that widespread adoption of LND for ICC remains low.[40] In turn, despite aggregating data from an international multi-institutional database, the relative number of patients included in the final analyses was somewhat small. In addition, due to the retrospective nature of the study, selection bias and residual confounding may have also affected patient selection for surgery, such as the indication for LND. While tLND was assessed relative to LN location in or beyond the hepato-duodenal ligament, further information on other lymph node station locations was not available.

Conclusion

In conclusion, central type ICC had very distinct clinicopathologic features compared with peripheral type ICC. For patients with central type ICC who were at high risk of LNM preoperatively, LND that included $\geq$3 nodes from the HDL and/or other nodal basins was associated with a survival benefit. In contrast, for patients with peripheral type ICC, as well as individuals with low-risk of LNM had no therapeutic benefit from LND.

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Conflict of interest

None declare.

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Appendix A. Supplementary data

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