Original article

Trends in use of lymphadenectomy in surgery with curative intent for intrahepatic cholangiocarcinoma

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Background: **The role of routine lymph node dissection (LND) in the surgical treatment of intrahepatic cholangiocarcinoma (ICC) remains controversial. The objective of this study was to investigate the trends of LND use in the surgical treatment of ICC.**

Methods: **Patients undergoing curative intent resection for ICC in 2000–2015 were identified from an international multi-institutional database. Use of lymphadenectomy was evaluated over time and by geographical region (West *versus* East); LND use and final nodal status were analysed relative to AJCC T categories.**

Results: **Among the 1084 patients identified, half (535, 49·4 per cent) underwent concomitant hepatic resection and LND. Between 2000 and 2015, the proportion of patients undergoing LND for ICC nearly doubled: 44·4 per cent in 2000 *versus* 81·5 per cent in 2015 ($P < 0·001$). Use of LND increased over time among both Eastern and Western centres. The odds of LND was associated with the time period of surgery and the extent of the tumour/T status (referent T1a: OR 2·43 for T2, $P = 0·001$; OR 2·13 for T3, $P = 0·016$). Among the 535 patients who had LND, lymph node metastasis (LNM) was noted in 209 (39·1 per cent). Specifically, the incidence of LNM was 24 per cent in T1a disease, 22 per cent in T1b, 42·9 per cent in T2, 48 per cent in T3 and 66 per cent in T4 ($P < 0·001$). AJCC T3 and T4 categories, harvesting of six or more lymph nodes, and presence of satellite lesions were independently associated with LNM.**

Conclusion: **The rate of LNM was high across all T categories, with one in five patients with T1 disease having nodal metastasis. The trend in increased use of LND suggests a growing adoption of AJCC recommendations in the treatment of ICC.**

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Introduction

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver cancer, and its incidence is increasing worldwide[1]. Resection of the primary ICC tumour site within the liver represents the best curative treatment option. The role of lymph node dissection (LND) at the time of surgery remains controversial, with some centres considering it standard whereas other surgeons perform LND only in selective circumstances[2,3]. When lymphadenectomy is performed, the incidence of lymph node metastasis (LNM) ranges from 17 to 62 per cent[4–9]. In turn, LNM has been strongly associated with long-term prognosis[5–9]. Specifically, the 5-year survival rate in patients with LNM ranges from 0 to 20 per cent, and 'true' long-term survival among patients with LNM is uncommon[5–9]. In addition, although patients with Nx and N1 disease have comparable disease-specific survival in the short term, those with Nx status who survive past 18 months have a survival comparable to that of patients with N0 disease[7]. As such, lack of nodal staging may lead to heterogeneous and potentially incorrect prognostic classification of patients with ICC.

Use of LND may vary not only among different institutions, but also by geographical region. Specifically, data from Eastern and Western centres have noted a variation in the use of lymphadenectomy ranging from 27 to 100 per cent[8,10]. Although several case series from Asia have noted that most centres do not regularly perform LND[4,11–13], other data from the West suggest that the procedure may be becoming more routine[5–9,14]. Despite the lack of consensus among surgeons, the AJCC staging manual recommends that the nodal basin be staged. Disease-specific staging for ICC was first introduced in the seventh edition of the AJCC manual, published in 2010[15]. The newly updated eighth edition of the AJCC staging system now recommends that six lymph nodes be evaluated to stage a patient with ICC[16].

Given that staging of ICC was introduced only within the past decade, the impact of formal recommendations to evaluate the nodal basin has not been well defined. Specifically, whether use of LND for ICC has evolved over time has not been examined. Many previous studies[4,11–14] have been single-centre reports with a small number of patients, or have included patients exclusively from either the East or the West. Therefore, the objective of the present study was to define trends in the use of LND among patients with ICC undergoing hepatectomy with curative intent using a large international experience. In addition, geographical variations in LND among Eastern and Western centres were characterized, and the number of lymph nodes examined over time was delineated in light of the AJCC recommendations.

Methods

Patients with ICC who underwent hepatectomy with curative intent between 2000 and 2015 were identified from a database involving 15 major hepatobiliary centres in America, Europe, Australia and Asia. All patients were diagnosed with ICC confirmed by histological examination. Patients who had a non-curative resection (R2), and those who underwent only ablation or intra-arterial therapies, were

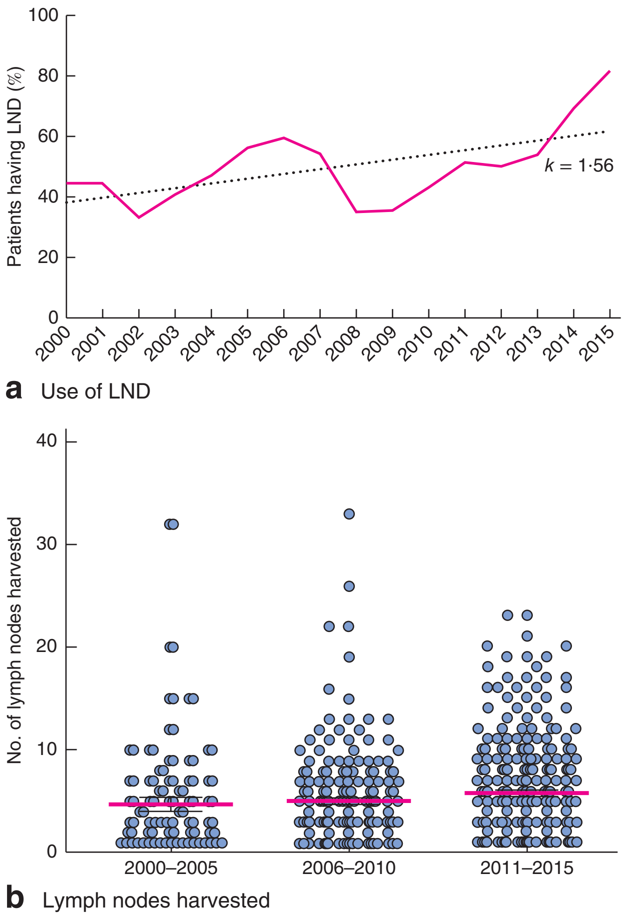


Fig. 1 Trends in use of **a** lymph node dissection (LND) and **b** number of lymph nodes evaluated as part of surgical management of intrahepatic cholangiocarcinoma: 2000–2005 (65 patients), 2006–2010 (188 patients) and 2011–2015 (282 patients). **b** Mean(s.d.) values are shown as well as individual patient numbers. $P = 0{\cdot}040$ (Kruskal–Wallis test)

excluded. The Institutional Review Board of each participating institution approved the study.

Data collection

Standard patient demographic and clinicopathological data were collected, including age, sex, serum level of carbohydrate antigen 19-9 and carcinoembryonic antigen. Tumour-related characteristics, including tumour diameter, number, location, morphology, histological grade, invasion of adjacent organs, major vascular and biliary invasion, microvascular/perineural invasion, satellite lesions, number of LNs harvested and number of metastatic LNs, were collected based on final pathology. Tumour stage was categorized according to the eighth edition of the AJCC manual[16]. Treatment-related data, including type and extent of hepatic resection, lymphadenectomy, duration of surgery and intraoperative blood loss, were collected based on operative and anaesthetic reports. Major hepatectomy was defined as the resection of three or more segments, minor hepatectomy as resection of one or two segments, and non-anatomical wedge resection according to the classification of Couinaud.

Statistical analysis

Continuous variables are expressed as mean(s.d.) or median (i.q.r.) values and compared with the Mann–Whitney *U* test or Kruskal–Wallis test as appropriate. Categorical variables are expressed as numbers and percentages, and compared with the χ^2 test or Fisher's exact test. Overall survival (OS) was evaluated using the Kaplan–Meier method and compared with the log rank test. In all analyses, two-tailed $P < 0{\cdot}050$ was considered statistically significant. Bonferroni correction was applied for the comparison of clinical characteristics among patients with ICC treated in different time periods (significance threshold, $P = 0{\cdot}050$ divided by the number of groups tested: $P = 0{\cdot}017$). A logistic multivariable regression model was used to identify independent predictors of LNM and the choice to perform a lymphadenectomy. Odds ratios (ORs) and 95 per cent confidence intervals were calculated, and $P < 0{\cdot}050$ was considered statistically significant. Receiver operating characteristic (ROC) curves and area under the curve (AUC) were used to assess the performance of the risk prediction models. Internal validation of the predictive model was assessed by the bootstrap resampling method. Bootstrap validation is a method of randomly resampling, with replacement, from an original data set for use in obtaining statistical inference[17]. All statistical analysis was carried out using SPSS® version 22.0 (IBM, Armonk, New York, USA).

Results

In total, 1084 patients with ICC undergoing surgery with curative intent were included (*Table S1*, supporting

Table 1 Logistic regression analysis of preoperative and intraoperative factors associated with the decision to perform lymphadenectomy

	Univariable analysis		Multivariable analysis	
	Odds ratio	*P*	Odds ratio	*P*
Time interval (years)				
2000–2005	1·00 (reference)		1·00 (reference)	
2006–2010	0·84 (0·62, 1·22)	0·376	1·54 (0·95, 2·27)	0·098
2011–2015	1·63 (1·12, 2·34)	0·021	2·84 (1·67, 4·42)	< 0·001
Geographical region		< 0·001		0·298
East	1·00 (reference)		1·00 (reference)	
West	2·21 (1·69, 2·88)		1·22 (0·78, 1·67)	
Tumour size (cm)				
< 5	1·00 (reference)		1·00 (reference)	
5–10	1·54 (1·21, 2·01)	0·003	1·01 (0·73, 1·62)	0·885
> 10	1·64 (1·12, 2·44)	0·018	1·03 (0·64, 1·85)	0·843
AJCC T status				
T1a	1·00 (reference)		1·00 (reference)	
T1b	1·73 (1·21, 2·63)	0·006	1·41 (0·79, 2·67)	0·135
T2	4·21 (3·01, 6·02)	< 0·001	2·43 (1·42, 4·21)	0·001
T3	3·03 (1·89, 4·72)	< 0·001	2·13 (1·19, 3·76)	0·016
T4	2·31 (1·33, 4·01)	0·003	1·02 (0·51, 2·17)	0·963
Clinical jaundice	2·67 (1·67, 4·32)	< 0·001	1·03 (0·68, 1·94)	0·880
Multiple tumours	1·72 (1·24, 2·39)	0·001	1·22 (0·83, 1·86)	0·400
Bilobar tumours	1·92 (1·41, 2·69)	< 0·001	1·10 (0·81, 1·72)	0·496
Major vascular invasion	3·33 (2·21, 4·92)	< 0·001	0·89 (0·47, 2·12)	0·745
Biliary invasion	4·69 (3·02, 7·27)	< 0·001	2·81 (1·51, 5·04)	0·001
Direct invasion of adjacent organs	0·94 (0·62, 1·48)	0·803		
Satellite lesions	1·21 (0·89, 1·63)	0·211		
Surgical procedure		< 0·001		< 0·001
Minor hepatectomy	1·00 (reference)		1·00 (reference)	
Major hepatectomy	4·21 (3·22, 5·65)		2·67 (1·86, 3·78)	
Major vascular resection	3·13 (2·01, 4·77)	< 0·001	1·81 (0·99, 3·23)	0·058
Bile duct resection	5·10 (3·38, 7·52)	< 0·001	1·91 (1·13, 3·19)	0·016

Values in parentheses are 95 per cent confidence intervals.

Table 2 Characteristics of patients undergoing hepatic resection for intrahepatic cholangiocarcinoma in Eastern and Western centres from 2008 to 2015

	East (*n* = 355)	West (*n* = 500)	*P*†
Age (years)*	55 (47–62)	63 (54–71)	< 0·001‡
Sex ratio (M : F)	247 : 108	253 : 247	< 0·001
Tumour size (cm)*	5·5 (3·9–7·4)	6·0 (4·0–9·0)	0·005‡
Multiple lesions (≥ 2)	25 (7·0)	104 (20·8)	< 0·001
Bilobar tumour	23 (6·5)	115 (23·0)	< 0·001
Vascular invasion			
Macro	43 (12·1)	84 (16·8)	0·063
Micro	64 (18·0)	191 (38·2)	< 0·001
Perineural invasion	22 (6·2)	141 (28·2)	< 0·001
Biliary invasion	33 (9·3)	62 (12·4)	0·155
Direct invasion of adjacent organs	10 (2·8)	40 (8·0)	< 0·001
Satellite lesions	65 (18·3)	117 (23·4)	0·071
AJCC T status			< 0·001
T1a	100 (28·2)	87 (17·4)	
T1b	91 (25·6)	99 (19·8)	
T2	97 (27·3)	224 (44·8)	
T3	57 (16·1)	50 (10·0)	
T4	10 (2·8)	40 (8·0)	
AJCC N status			< 0·001
N0	63 (17·7)	191 (38·2)	
N1–2	55 (15·5)	111 (22·2)	
Nx	237 (66·8)	198 (39·6)	
Histological grade			< 0·001
Well to moderate	337 (94·9)	302 (60·4)	
Poor to undifferentiated	17 (4·8)	107 (21·4)	
Missing	1 (0·3)	91 (18·2)	
Morphological type			0·007
Mass-forming ± periductal infiltrating	345 (97·2)	440 (88·0)	
Papillary/periductal infiltrating	10 (2·8)	34 (6·8)	
Missing	0 (0)	26 (5·2)	
Resection procedure			< 0·001
Minor	259 (73·0)	95 (19·0)	
Major	96 (27·0)	336 (67·2)	
Missing	0 (0)	69 (13·8)	
Surgical margin			< 0·001
R0	346 (97·5)	412 (82·4)	
R1	9 (2·5)	88 (17·6)	
Major vascular resection	40 (11·3)	47 (9·4)	0·872
Bile duct resection	30 (8·5)	89 (17·8)	< 0·001
Lymphadenectomy	118 (33·2)	302 (60·4)	< 0·001
Intraoperative blood loss (ml)*	250 (150–500)	500 (300–800)	< 0·001‡
Duration of surgery (min)*	120 (90–168)	270 (200–360)	< 0·001‡
Postoperative complications	106 (29·9)	202 (40·4)	< 0·001
Clavien–Dindo classification			0·003
I–II	75 (21·1)	103 (20·6)	
III–IV	26 (7·3)	76 (15·2)	
V	5 (1·4)	23 (4·6)	
90-day mortality	15 (4·2)	31 (6·2)	0·093

Values in parentheses are percentages unless indicated otherwise; *values are median (i.q.r.). †χ^2 or Fisher's exact test, except ‡Mann–Whitney *U* or Kruskal–Wallis test.

information). Median patient age was 60 (i.q.r. 51–69) years; there were 606 men (55·9 per cent) and 478 women (44·1 per cent). At the time of surgery, 535 patients (49·4 per cent) had at least one lymph node harvested, although the exact number of lymph nodes evaluated was available for only 529 patients. The median number of lymph nodes evaluated was 4 (i.q.r. 2–8); 325 patients (30·0 per cent) had one to five nodes evaluated, and 204 (18·8 per cent) had six or more nodes evaluated. LNM was noted in 209 (39·1 per cent) of the 535 patients who underwent LND; the most common site of metastasis was the hepatoduodenal ligament (151 patients, 72·2 per cent). Not surprisingly, median OS was worse among patients with N1 disease (18·0 months, compared with 50·0 months in those with N0 disease; $P < 0{\cdot}001$). Patients who did not undergo lymphadenectomy (Nx status) had an intermediate prognosis (median OS 43·0 months *versus* 50·0 months for N0 disease; $P = 0{\cdot}035$) (*Fig. S1*, supporting information).

Trends in use of lymphadenectomy

Between 2000 and 2015, the proportion of patients undergoing LND for ICC nearly doubled (44·4 per cent in 2000 *versus* 81·5 per cent in 2015; $P < 0{\cdot}001$) (*Fig. 1a*). In total, 65 (46·1 per cent) of 141 patients underwent LND in 2000–2005, 188 (41·9 per cent) of 449 in 2006–2010, and 282 (57·1 per cent) of 494 in 2011–2015 ($P < 0{\cdot}001$) (*Fig. 1b*), which translated into a consistent upward trend in LND from 2000 to 2015 (slope 1·56) (*Fig. 1a*). Baseline characteristics of patients changed over the time periods examined. Specifically, patients treated in the early period (2000–2005) had more advanced disease at presentation: 70·2 per cent had T2–4 disease in 2000–2005, compared with 57·0 per cent in 2006–2010 and 57·3 per cent in 2011–2015 (both $P < 0{\cdot}010$) (*Table S1*, supporting information). Consistent with the lower proportion of advanced disease, the extent of hepatectomy (minor resection: 20·6 per cent in 2000–2005 *versus* 40·8 per cent in 2006–2010 and 39·5 per cent in 2011–2015; both $P < 0{\cdot}010$) as well as intraoperative blood loss, duration of surgery and in-hospital mortality all decreased over time (all $P < 0{\cdot}010$).

In multivariable analysis, several factors were associated with the performance of LND (*Table 1*). Most notably, the odds of lymphadenectomy were strongly associated with the period during which the patient underwent surgical resection (2011–2015 *versus* 2000–2005: OR 2·84, $P < 0{\cdot}001$). In addition, use of LND was associated with the extent of the tumour/T category. For example, among patients who had LND, 28·6 per cent (63 of 220) had T1a disease, 41·2 per cent (93 of 226) had T1b, 62·8 per cent (273 of 435) had T2, 54·6 per cent (71 of 130) had T3, and 48 per cent (35 of 73) had T4 disease. When different T categories were assessed in multivariable analysis, after controlling for competing risk factors, T status remained independently associated with the odds of undergoing LND (referent T1a: T2 disease, $P = 0{\cdot}001$; T3 disease, $P = 0{\cdot}016$) (*Table 1*). Other factors associated with use of LND included tumour-specific factors such as the presence of biliary invasion (OR 2·81, 95 per cent c.i. 1·51 to

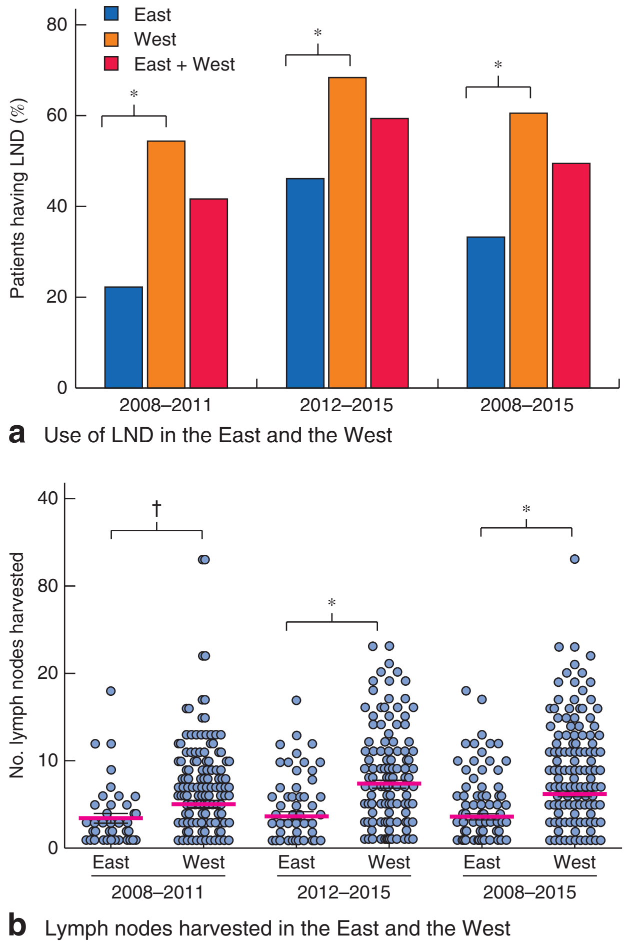
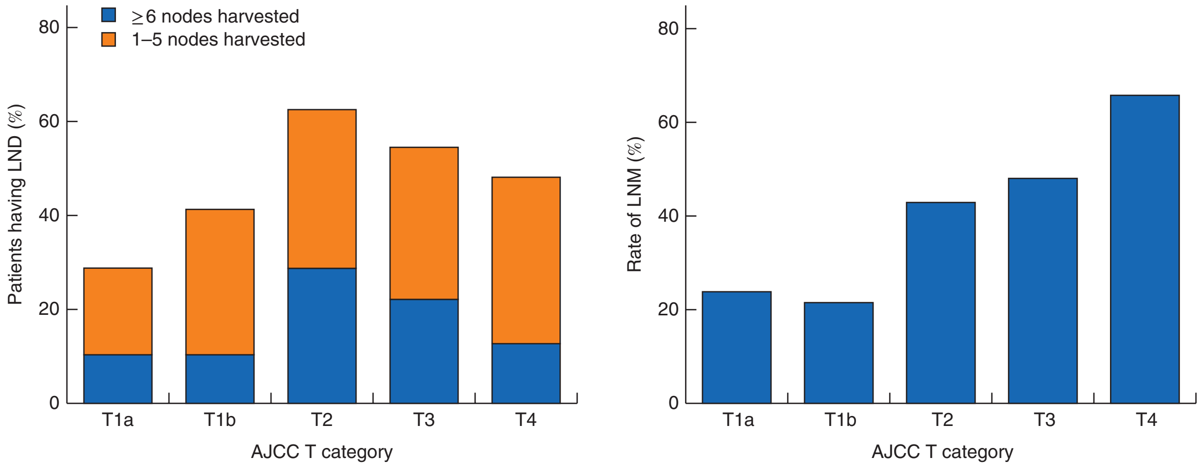


Fig. 2 Trends in **a** lymph node dissection (LND) and **b** number of lymph nodes harvested as part of surgical management of intrahepatic cholangiocarcinoma stratified by Eastern and Western centres: 2008–2011 (East 42, West 153 patients), 2012–2015 (East 76, West 149) and 2008–2015 (East 118, West 302). **b** Mean(s.d.) values are shown as well as individual patient yields. *$P < 0{\cdot}001$, †P 0·033 (Kruskal–Wallis test)

5·04; $P = 0{\cdot}001$) and technical factors such as major hepatectomy (OR 2·67, 1·86 to 3·78; $P < 0{\cdot}001$), as well as vascular (OR 1·81, 0·99 to 3·23; $P = 0{\cdot}058$) and bile duct (OR 1·91, 1·13 to 3·19; $P = 0{\cdot}016$) resection.

Lymphadenectomy in Eastern *versus* Western centres

In 2008–2015, the period for which data on both Eastern and Western patients (855) were available, 355 patients (41·5 per cent) from the East and 500 (58·5 per cent) from the West underwent resection with curative intent for ICC. Patients undergoing surgery in Eastern centres had



a LND according to AJCC category **b** Rate of LNM

Fig. 3 **a** Proportion of patients undergoing lymph node dissection (LND) and number of lymph nodes harvested during hepatic resection for intrahepatic cholangiocarcinoma, stratified by AJCC T category (eighth edition[16]). **b** Rate of lymph node metastasis (LNM) among patients who underwent LND stratified by AJCC T category

lower overall use of LND than patients treated in Western centres (33·2 *versus* 60·4 per cent respectively; OR 3·12, 95 per cent c.i. 2·31 to 4·14, $P < 0.001$) (*Table 2*). Use of LND increased over time in both Eastern and Western centres, but remained more prevalent among Western centres (2008–2011: 54·3 per cent in the West *versus* 22·1 per cent in the East, OR 4·19, 2·78 to 6·32, $P < 0.001$; 2012–2015: 68·3 *versus* 46·1 per cent respectively, OR 2·53, 1·67 to 3·82, $P < 0.001$) (*Fig. 2a,b*).

Tumours treated in Western *versus* Eastern centres had more aggressive characteristics, such as larger tumour size, more multiple lesions, higher frequency of adjacent organ invasion and more advanced T status (all $P < 0.010$) (*Table 2*), and also were more likely to require a major hepatic resection (67·2 per cent in Western *versus* 27·0 per cent in Eastern centres; $P < 0.001$). When these factors were controlled for in multivariable analysis, geographical region (West *versus* East) was no longer independently associated with the odds of LND use (OR 1·22, 95 per cent c.i. 0·78 to 1·67; $P = 0.298$).

Number of nodes evaluated and lymph node metastasis

Among patients who had LND, the number of lymph nodes evaluated increased over the intervals examined (median number of nodes evaluated: 3 (i.q.r. 1–7) in 2000–2005 *versus* 3 (2–7) in 2006–2010 *versus* 4 (2–8) in 2011–2015; $P = 0.040$) (*Fig. 1b*). The proportion of patients who had the recommended LND (6 or more nodes harvested) also increased over time: 12·8 per cent in 2000–2005 *versus* 14·5 per cent in 2006–2010 *versus* 24·5 per cent in 2011–2015 ($P < 0.001$) (*Table S1*, supporting information). Patients with T2 tumours were the most likely to have six or more lymph nodes evaluated (*Fig. 3a*). The median number of nodes evaluated was also higher among patients in the West (2008–2011: 4 (i.q.r. 2–7·5) in the West *versus* 2 (1–5) in the East, $P < 0.001$; 2012–2015: 6 (3–10) *versus* 2 (1–6) respectively, $P < 0.001$) (*Fig. 2b*).

In lymph node-positive patients, the median number of metastatic nodes did not change over time: 1 (i.q.r. 1–3) in 2000–2005 *versus* 1 (1–2) in 2006–2010 *versus* 2 (1–3) in 2011–2015 ($P = 0.921$). The lymph node ratio (ratio of metastatic nodes to total nodes evaluated) also did not change over time (median 0·6 (i.q.r. 0·2–1·0) in 2000–2005 *versus* 0·5 (0·3–1·0) in 2006–2010 *versus* 0·5 (0·2–1·0) in 2011–2015; $P = 0.504$). In multivariable analysis, several patient and tumour-specific factors were associated with the presence of LNM (*Table 3*). The odds of metastasis were higher among patients who had six or more nodes harvested (OR 1·63, 95 per cent c.i. 1·13 to 2·32; $P = 0.021$) and in tumours with satellite lesions (OR 1·77, 1·11 to 2·87; $P = 0.018$) (*Table 3*). Compared with patients who had T1a disease, patients with AJCC T3 (OR 2·21, 1·02 to 4·78; $P = 0.047$) and T4 (OR 3·82, 1·37 to 10·10; $P = 0.007$) status had higher odds of LNM.

Among patients who had lymphadenectomy, the rate of LNM was 24 per cent (15 of 63) for T1a disease, 22 per cent (20 of 93) for T1b, 42·9 per cent (117 of 273) for T2, 48 per cent (34 of 71) for T3 and 66 per cent (23 of 35) for T4 (*Fig. 3b*). In univariable analysis, the incidence of LNM increased incrementally as the T

Table 3 Logistic regression analysis of preoperative and intraoperative factors predicting lymph node metastasis

	Univariable analysis		Multivariable analysis	
	Odds ratio	*P*	Odds ratio	*P*
Age (years)	1·01 (0·95, 1·06)	0·123		
Sex (M *versus* F)	0·89 (0·65, 1·27)	0·548		
Clinical jaundice	2·10 (1·22, 3·64)	0·007	1·40 (0·84, 2·62)	0·255
Tumour size (cm)				
< 5	1·00 (reference)			
5–10	0·89 (0·61, 1·43)	0·673		
> 10	0·84 (0·49, 1·50)	0·541		
Multiple tumours	1·67 (1·11, 2·57)	0·014	1·11 (0·59, 1·78)	0·783
Bilobar tumours	1·41 (0·92, 2·10)	0·143		
Major vascular invasion	2·01 (1·32, 3·14)	0·001	1·33 (0·81, 2·21)	0·231
Biliary invasion	2·24 (1·39, 3·42)	< 0·001	1·64 (0·97, 2·57)	0·078
Satellite lesions	2·23 (1·47, 3·33)	< 0·001	1·77 (1·11, 2·87)	0·018
AJCC T status				
T1a	1·00 (reference)		1·00 (reference)	
T1b	0·87 (0·41, 1·89)	0·735	1·02 (0·35, 2·14)	0·921
T2	2·41 (1·33, 4·46)	0·006	1·67 (0·92, 3·36)	0·113
T3	2·93 (1·41, 6·22)	0·004	2·21 (1·02, 4·78)	0·047
T4	6·14 (2·51, 15·22)	< 0·001	3·82 (1·37, 10·10)	0·007
No. of lymph nodes harvested		0·005		0·021
1–5	1·00 (reference)		1·00 (reference)	
≥ 6	1·73 (1·18, 2·44)		1·63 (1·11, 2·32)	

Values in parentheses are 95 per cent confidence intervals.

category advanced (with T1a as referent: OR 2·41, 95 per cent c.i. 1·33 to 4·46 for T2, $P = 0{\cdot}006$; OR 2·93, 1·41 to 6·22 for T3, $P = 0{\cdot}004$; OR 6·14, 2·51 to 15·22 for T4, $P < 0{\cdot}001$) (*Table 3*). Prediction of LNM was modest, even when combining these independent factors into a risk score (AUC 0·687, Cox and Snell $R^2 = 0{\cdot}091$) (*Fig. S2*, supporting information).

Discussion

The role of lymphadenectomy for primary and secondary malignancies of the liver varies considerably. For example, LND is performed routinely for some primary malignancies such as fibrolamellar hepatocellular carcinoma and gallbladder cancer[2,18], yet not for other cancers such as standard hepatocellular carcinoma or metastatic disease to the liver[8,19,20]. Traditionally, the reasons for performing LND include accurate staging, as well as adequate clearance of the locoregional nodal basin. For most gastrointestinal malignancies, nodal evaluation represents a cornerstone of staging and accurate long-term prognostic stratification[6,9]. In addition, although clearance of the nodal basin is unlikely to provide a survival advantage, removal of lymph nodes may prevent locoregional recurrence, which can be a particular challenge when it occurs at the hepatic hilum. The role of routine LND in the surgical management of patients with ICC has been a topic of interest and debate, with no clear consensus[4–8,11–14,21]. A recent meta-analysis[8] evaluated the management of lymph nodes during hepatic resection for ICC. The authors advocated consideration of LND in the treatment of ICC, although the data were insufficient to recommend routine staging LND unequivocally[8]. In a separate study[22], an expert consensus panel recommended that regional LND should be considered as a standard part of surgical resection for ICC, especially in patients who are clinically node-negative and may have occult metastatic disease. The present study is important as it demonstrates empirically the growing widespread adoption of LND for ICC over the past 16 years. From 2000 to 2015, the proportion of patients undergoing LND for ICC nearly doubled. Use of LND increased over time among both Eastern and Western centres, and was no different among Eastern *versus* Western centres in multivariable analyses after controlling for tumour factors. In addition, the rate of LNM was 39·1 per cent and the presence of nodal metastasis could not be predicted accurately based on tumour factors. In fact, even patients with T1a disease had an LNM rate of 24 per cent.

In the present study, overall use of LND in the whole cohort was only 49·4 per cent. By 2015, however, eight of ten patients who underwent surgical resection of ICC had a concomitant LND. There was a consistent upward trend in the adoption of LND over the last one and a half decades.

The upward trend in LND was noted among centres in both the East and the West. These data collectively suggest a change as more and more surgeons are incorporating routine LND into the surgical management of patients with ICC. In addition, the number of lymph nodes evaluated increased over time, with an increasing proportion of patients having the recommended number of six or more nodes harvested. Despite this increase in the number of lymph nodes evaluated, even in 2015 only 44 per cent of patients (24 of 54) had at least six nodes evaluated.

Several preoperative and intraoperative tumour characteristics were strongly correlated with LNM, consistent with data from previous studies[5,23]. These factors included the presence of satellite lesions, as well as the number of nodes evaluated. In particular, patients who had the recommended number of at least six lymph nodes harvested had a roughly 60 per cent increased odds of LNM. Advanced T category was also associated with an incremental increased odds of LNM. Using clinical and tumour-specific factors, prediction of LNM was poor, suggesting that selective LND may not be effective. Some investigators[4,24,25] have suggested that LND may be necessary only in patients with advanced disease, but the present study observed LNM even among patients with early-stage disease. Specifically, LNM occurred in one-fifth of patients with ICC who had a very early T category (T1a and T1b), and in more than 40 per cent of patients with T2 disease. The accuracy of preoperative imaging assessment of LNM by CT or MRI is low, with a sensitivity of only 40–50 per cent and specificity of 77–92 per cent[26,27]. Although detection of LNM may be improved by preoperative fluorodeoxyglucose (FDG)-PET, the overall accuracy remains poor[27]. Given the poor accuracy of preoperative clinical staging, as well as the poor performance of prediction models to identify patients at highest risk of LNM, routine histological assessment with LND appears to be the only accurate way to diagnose LNM[9,26]. Routine dissection of the nodal basin, including station 12 (hepatoduodenal), station 8 (common hepatic artery) and station 13 (posterior to pancreas) nodes, should therefore be performed. For left-sided tumours, station 7 (left gastric artery) and station 1 (right oesophageal crus) should also be considered. Finally, in a small subset of patients, preoperative imaging such as FDG-PET may indicate a metastatic node in the supradiaphragmatic area (station 110), which then should be removed.

As noted previously, the status of the nodal basin is an important prognostic factor among patients with ICC[5–9,28,29]. In addition to tumour characteristics such as tumour size, lesion number and vascular invasion, LNM has consistently been identified as one of the strongest prognostic factors associated with long-term outcomes of patients with ICC[5–9,12–14,29]. Leaving the nodal basin unstaged can lead to prognostic uncertainty for the patient, as well inhibit postoperative discussions on the need for adjuvant therapy. For example, in the present study, patients who did not have staging LND (Nx status) had a worse long-term survival than patients who had documented node-negative disease from an LND. Patients with Nx disease have been reported previously[7] to have a worse survival within the first 18 months after surgery than patients with N0 disease, although those who survived longer than 18 months had a similar long-term outcome to those with N0 disease. Some authors[4,11,12,29] have advocated against routine LND for ICC because OS was no different among patients who did and those who did not have LND. However, like other gastrointestinal malignancies, LND is performed largely with the goal of facilitating accurate staging, as well as to inform adjuvant recommendations. Although adjuvant chemotherapy may not improve the long-term prognosis of 'all-comers' following surgical resection, adjuvant therapy may be associated with a potential survival benefit in selected subgroups of patients at increased risk of recurrence. Specifically, among patients with N1 disease, those who received adjuvant chemotherapy had a better 5-year OS[30]. Taken together, these studies highlight that routine LND should be performed to achieve complete resection of ICC, clear the locoregional LN basin, provide accurate staging, and inform discussions about adjuvant therapy.

Several limitations need to be considered. Given the relative rarity of ICC, data had to be accrued over a long period at multiple centres. In addition, Eastern centres entered the international consortium only in 2008, and thus data on both Eastern and Western centres were available only for the later intervals. However, when only patients from Western centres were evaluated, the data remained consistent (*Fig. S3*, supporting information). The study design was also retrospective in nature and included only patients who had resection. Selection bias was thus possible, as patients who had bulky nodal disease on preoperative imaging may not have been offered an operation. Preoperative imaging data were not available for all patients, and therefore preoperative clinical stage was not known. The indication for LND was also unknown and may have been due to preoperative imaging, enlarged nodes on exploration, or surgeon preference. Having data on all patients who underwent resection of ICC allowed trends of LND to be assessed over time. The finding that the rate of LNM did not change over time, whereas the rate of LND use did, strongly suggests a change in surgeon preference as the reason for the increase in LND.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.