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ORIGINAL ARTICLE

Management of Lymph Nodes During Resection of Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma: A Systematic Review

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Abstract The role of lymph node dissection (LND) in the treatment of patients with hepatocellular carcinoma (HCC) or intrahepatic cholangiocarcinoma (ICC) remains controversial. We sought to systematically review all available evidence to determine the role of LND in patients with HCC and ICC. Studies that reported on LND, lymph node metastasis (LNM), and short- and long-term outcomes for patients with HCC or ICC survival were identified from PubMed, Cochrane, Embase, Scopus, and Web of Science databases. Data were extracted, synthesized, and analyzed using standard techniques. A total of 603 and 434 references were identified for HCC and ICC, respectively. Among HCC patients, the overall prevalence of LND was 51.6 % (95 % confidence interval (CI) 19.7-83.5) with an associated LNM incidence of 44.5 % (95 % CI 27.4–61.7). LNM was associated with a 3- and 5-year survival of 27.5 and 20.8 %, respectively. Among ICC patients, most patients 78.5 % (95 % CI 76.2–80.7) underwent LND; 45.2 % (95 % CI 39.2–51.2) had LNM. Three and 5-year survival among ICC patients with LNM was 0.2 % (95 % CI 0–0.7) and 0 %, respectively. While there are insufficient data to recommend a routine LND in all patients with HCC or ICC, the potential prognostic value of LND suggests that LND should at least be considered at the time of surgery.

Keywords Intrahepatic cholangiocarcinoma · Hepatocellular carcinoma · Lymphadenectomy

Introduction

Liver cancer is the fifth most common neoplasm worldwide with nearly 750,000 new cases and nearly 700,000 deaths estimated in 2008 alone.[1] Among primary liver cancer cases, the two most common forms are hepatocellular carcinoma (HCC), accounting for 70–85 % of primary liver cancer cases,[2] and intrahepatic cholangiocarcinoma (ICC) representing 10–15 % of all primary liver cases.[3,4] Nearly one half of all HCC cases in the USA are attributable to viral hepatic infection (HBV or HCV).[5–10] Rising rates of obesity have also caused a surge in nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH), which have been found to be independent risk factors for the development of HCC.[8,11–16] Risk factors for ICC, on the other hand, are less well understood but include the presence of intrahepatic stones and primary sclerosing cholangitis.[17,18]

Prognosis in patients with primary liver cancer is poor. Median survival after diagnosis with HCC is estimated between 1 to 60 months depending on the stage of disease at presentation with an estimated overall 5-year survival of 12–28 %.[19–22] Similarly, patients with ICC have an estimated median survival of only 18–39 months and an estimated 5-year survival between 25–40 %.[23–25] Though complete surgical resection provides the best option for long-term survival,[26,27] only 22–30 % of patients with HCC and 30–54 % of patients with ICC are eligible for curative-intent resection at the time of presentation.[19,28–30] Prognosis after surgical resection is heavily influenced by several tumor-specific characteristics in patients with HCC including tumor size, the presence of minor or major vascular invasion, and lymph node metastasis (LNM).[26,31,32] Similarly, factors

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with prognostic significance after ICC resection are the presence of vascular invasion, multiple tumors, and LNM.[17,33,34] In fact, LNM has been found to be one of the most important adverse prognostic factors in patients with HCC and ICC.[35–37] Despite this, the utility of a formal evaluation of lymph node involvement at the time of surgery has been debated.

The importance of performing a lymph node dissection (LND) in an oncological resection has been established for several other hepato-pancreato-biliary tumors including extrahepatic cholangiocarcinoma,[38] gallbladder cancer,[39] and fibrolamellar HCC.[40] However, the benefit of performing an LND during surgical resection for primary liver cancer remains controversial. Several authors have advocated for routine LND in order to comprehensively evaluate the extent of disease and accurately stage patients.[25,41] Others have reported an association with LND and increased survival,[42] possibly through improved locoregional tumor control.[43] Conversely, several authors have found that an LND provides no survival benefit,[44,45] and that the dissection only adds to the complexity and morbidity of the operation.[35]

In this context, we sought to systematically review all available evidence to determine the utility of performing an LND in patients with HCC and ICC. Furthermore, we aimed to identify all studies evaluating the prognostic importance of LNM in patients undergoing curative-intent resection for HCC and ICC.

Materials and Methods

Search Strategy

A systematic search of the literature was performed for studies published until December 31, 2013 using the following databases: PubMed, Cochrane, Embase, Scopus, and Web of Science. The following search terms were used to identify all articles relevant to our study: ("carcinoma, hepatocellular"[46]) OR (hepatocellular [tiab] AND (cancer* [tiab] OR neoplasm* [tiab] OR carcinoma* [tiab] OR tumor* [tiab] OR tumour* [tw]) OR ("intrahepatic cholangiocarcinoma") OR ("carcinoma, intrahepatic bile duct") OR ("intrahepatic biliary duct carcinoma") AND ("lymph node excision"[46] OR "lymph node excisions" OR "lymphadenectomy" OR "lymphadenectomies" OR "lymph node dissection"). Equivalent search strategies were used in the Embase and Web of Science databases.

Inclusion and Exclusion Criteria

All randomized controlled trials and cohort studies that evaluated the impact of LND on clinical outcomes in patients undergoing curative intent surgery for HCC and ICC were included in the study. Studies including patients with fibrolamellar HCC were excluded from the analysis. Articles were also excluded if they did not contain sufficient information regarding the incidence of LND within the cohort. Furthermore, studies with low sample size (<10 patients), limited follow-up time (<1 year), or insufficient operative data (type and extent of hepatic resection and LND) were also excluded.

Data Extraction, Synthesis, and Analysis

Using a custom-designed data extraction form, the following data from each study were extracted: study period, country of origin, and design as well as standard demographic and clinical characteristics of the cohort (number of patients and age), treatment characteristics (use of perioperative therapy, type, and extent of hepatic resection and LND), pathologic information (total number of lymph nodes harvested, number of positive lymph nodes, and lymph node ratio), and clinical outcomes (post-operative complications, overall survival, intrahepatic recurrence, LN recurrence, and total recurrence rate). The overall incidence of LNM was calculated by dividing the number of patients with metastatic lymph nodes by the number of patients who underwent LND. A second reviewer independently reviewed all articles and checked all extracted data for accuracy.

Statistical Analysis

The aggregated proportional variables (LND, LNM, recurrence, morbidity, and survival) were computed by "metan" or "meta" command which is an average of proportions weighted by the inverse of their variances. The fix/random model described by DerSimonian and Laird[47] was used to calculate pool estimation based on the Q^2 and I^2 heterogeneity test results. For Q statistics, due to the low power of this test, a minimum P value cutoff of 0.1 was established as a threshold of heterogeneity. For I^2 results, values of approximately 25, 50, and 75 % were interpreted as low, medium, and high heterogeneity, respectively.[48] The standard error (Se_i) for each proportional variable (pi) was computed using the binominal distribution

$$\mathrm{Se_i} = \sqrt{\frac{pi(1-pi)}{ni}}$$

The Z value for comparing two weighted pooled proportions was computed according to the following formula:

$$\mathrm{Z\ value} = \frac{Survival1 - survival\ 2}{\sqrt{var(survival\ 1) + var(survival2)}}$$

The total number of lymph nodes examined (TNLE) was reported as mean and standard deviation. When studies reported this variable as median and range, the mean and variance were estimated by taking into account the sample size as proposed by Hozo et al.[49] Pooled estimations were made if at

least three articles were available.[50] All statistical analyses were performed using STATA version 10.0 (Stata Corp LP, College Station, TX, USA).

Results

Hepatocellular Carcinoma

Search Results and Article Review

We identified 603 studies through searches of PubMed (104), Embase (209), Cochrane (0), Scopus (140), and Web of Sciences (150) databases. Case reports (20), review articles (14), duplicate references (279), and non-English texts (38) were excluded. After abstract reviewing, 242 of the 252 original articles found were eliminated for failure to meet inclusion criteria. In addition, three additional studies were omitted after full-text review due to incomplete data and failure to meet inclusion criteria (Fig. 1a).[51–53] Ultimately, seven studies (four prospective cohort studies[41,54–56] and three retrospective studies[42,45,57]) were considered for final analysis (Table 1). No randomized controlled trials comparing liver resection alone and liver resection with LND were identified.

Description of New Historical Cohort

In our new historical cohort a total of 5,844 patients underwent surgical resection for HCC between 1982 and 2012. Mean age was 59.4 years (SD±5.60). In aggregate, 51.6 % of patients (95 % confidence interval (CI) 19.7–83.5) underwent LND at the time of resection. Among those who underwent LND, the most common site for LND was along the common hepatic artery (91.9 %) followed by dissection of the hepatic pedicle (50.0 %) and retro-pancreatic space (39.4 %). Among patients with at least one lymph node evaluated, 44.5 % (95 % CI 27.4–61.7) had evidence of LNM on pathologic examination. The aggregate mean TNLE was 6.4 (95 % CI 1.8–11.1). The lymph node ratio (LNR), or the proportion of LNM to TNLE, was reported as 0.39 (77/195) in one study[57] and 0.12 (439/3,433) in another.[56]

Effect of LNM and LND on Survival, Recurrence, and Mortality

Three studies,[45,56,57] involving 3,520 (60.2 %) patients, compared survival among patients with and without LNM (Table 2). Patients with LNM had worse 3- (27.5 %, 95 % CI 13.1–41.8 %) and 5-year survival (20.8 %, 95 % CI 13.2–28.4 %) compared with patients without LNM (3-year survival 60.2 %, 95 % CI 52.8–67.5 %; 5-year survival 42.6 %, 95 % CI 36.6–48.6 %) ($P<0.001$) (Fig. 2a)

Two studies[42,57] reported the effect of LND on survival among patients with radiographic or biopsy-proven LNM and found a higher median survival among patients who underwent a LND (P value <0.05). No comparisons, however, were made between patients who underwent LND and those who did not undergo LND. Among those who underwent LND, aggregate morbidity was 21.4 % (95 % CI 18.2–24.6), whereas mortality was 20.8 % (95 % CI 0–43.8). There were insufficient data among the articles reviewed to calculate aggregate morbidity and mortality among patients who did not undergo LND.

Intrahepatic Cholangiocarcinoma

Search Results and Study Selection

We identified 434 articles from searches of PubMed (151), Embase (151), Scopus (43), and Web of Science (89) databases. In a preliminary literature review, duplicate references (162), case reports (16), review articles (7), and non-English articles (24) were excluded. After abstract screening, 181 articles did not fulfill the inclusion criteria and were omitted. Additionally, after full-text review, eight articles[58–65] were omitted because they did not report on the incidence of LND, and five articles[35,66–69] were excluded because they did not differentiate between hepatic lymph node sampling and LND (Fig. 1b). Ultimately, 21 studies (6 prospective[43,44,70–73] and 15 retrospective[17,25,34,72,74–84]) were included in the final analysis; no randomized controlled trials comparing ICC resection with and without LND were found (Table 3).

Ten articles [25,71,74–77,79,80,82,84] consisting of 1,033 (43.8 %) patients reported on preoperative TNM stage. The majority of patients had either advanced stage III (22.4 %, 95 % CI 9.1–35.8 %) or stage IV (36.2 %, 95 % CI 28.0–44.4 %) disease; the remaining patients had early stage I (18.7 %, 95 % CI 11.2–.26.1 %) or stage II (24.2 %, 95 % CI 19.2–29.2 %) disease. The use of neoadjuvant chemotherapy was reported in only one study[83] among which 11 % of patients ($n=5$) received preoperative treatment.

Description of New Historical Cohort

A total of 2,358 patients underwent resection for ICC from 1973 to 2012 and were included in the analysis. The mean age was 62.4 (SD±3.2) years. Among the entire cohort, 78.5 % (95 % CI 76.2–80.7) of patients underwent LND, and 45.2 % (95 % CI 39.2–51.2) of these had LNM. The mean TNLE was 13.8 (95 % CI 9.2–18.41). The most common site of LND was the

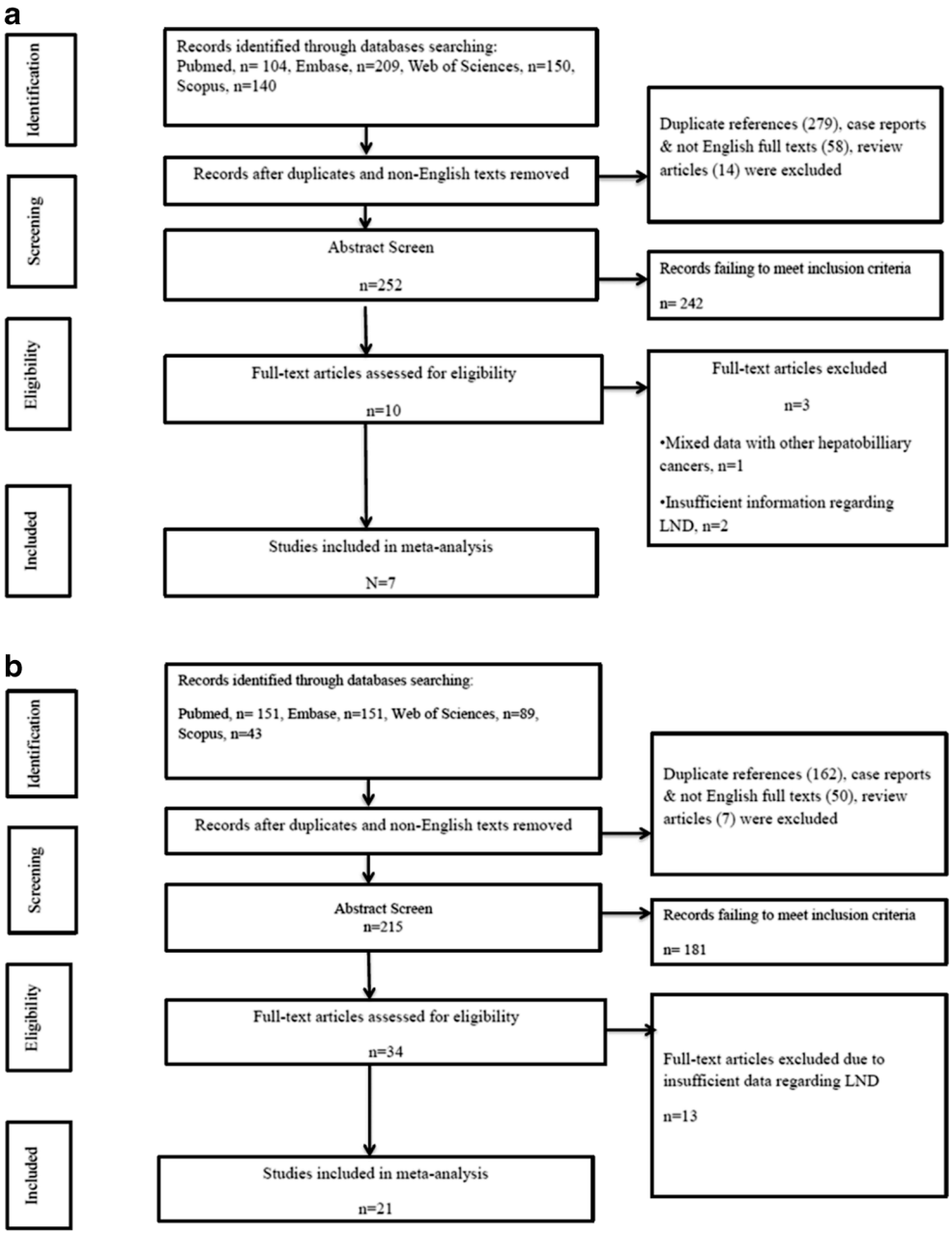

Fig. 1 Flow chart of search and selection strategy for studies involving **a** hepatocellular carcinoma (HCC) or **b** intrahepatic cholangiocarcinoma (ICC)

hepatoduodenal ligament (44.5 %, 95 % CI 37.9–51.1) followed by the common hepatic artery (95 % CI 6.5–12.5).[25,70,73,75,80–83]

LN Involvement and LND Effects on ICC Patients' Prognosis

Long-term survival of node-positive and node-negative patients was reported in eight studies[43,72,73,76,78,79,82,85] (Table 4). The 3- and 5-year survival of patients with LNM were 0.2 % (95 % CI 0–0.7) and 0 %, respectively, compared with 55.6 % (95 % CI 50.4–60.9) and 45.1 % (95 % CI 37.3–52.9) among patients without LNM ($P<0.001$) (Fig. 2b).

Four articles[72,75,76,78] reported the effect of LND on survival of patients with known LNM. Among these, three studies found no difference in survival between patients who underwent LND and those who did not undergo LND.[72,75,78] In contrast, one study[76] found an improved survival among patients who underwent LND versus those who did not (13 vs. 4 months; $P<0.001$). There were insufficient data to calculate pooled morbidity and mortality for ICC patients based on whether or not an LND was performed.

Table 1 Study characteristic for patients with hepatocellular carcinoma

Study name	Study characteristics	Number	Number of patients undergoing LND	Percent of patients with LNM	Mean TNLE	Location of LND	Previous therapy	Recurrence of LNM	Morbidity	Morbidity
Awazu	1998–2012 Japan Prospective	15	15/15 (100 %)	15/15 (100 %)	1.8	Hepatoduodenal ligament (29.6 %) Common hepatic artery (29.6 %) Retro-pancreatic space (18.5 %) Para-aortic area (7.4 %) Celiac trunk (7.4 %) Root of mesentery (3.7 %) Cervical area (3.7 %)	TACE (33.3 %) RFA (13.3) Partial hepatectomy (23 %) None (40 %)	4(26.6 %)	–	60 %
Ercolani	1999–2001 Italy Prospective	40	40/40 (100 %)	3/40 (7.5 %)	6.8	Retro-pancreatic space (59.2 %) Common hepatic artery (100 %) Hepatic pedicle (100 %) Celiac trunk (31 %) Left gastric artery (26 %)	Not mentioned	2 (66.60 %)	39.2 %[a]	[a]
Kobayashi	1992–2008 Japan Retrospective	2,189	18/2,189 (0.8 %)	18/18 (100 %)	–	Left gastric artery (26.6 %) Retro-pancreatic space (22.2 %) Para-aortic area (16.6 %) Hepatoduodenal ligament (16.6 %) Common hepatic artery (5. %) Others (13 %)	Hepatectomy (44 %) TAE (16 %) Percutaneous ethanol injection (5 %) Proton beam therapy (5 %) None (27.7 %)	12 (66 %)	33 %[a]	0 %[a]
Lee	1982–2005 Taiwan Retrospective	2,034	170/2,034 (8.3 %)	25/170 (14.7 %)	–	–	Not mentioned	15 (59 %)	–	–
Ravaioli	2001–2005 Italy Prospective	75	37/75 (49.3 %)	1/37 (2 %)	6.7	–	Not mentioned	22 (57 %)	33 %[a]	14 %[a]
Sun	1999–2005 China Retrospective	968	32/968(3 %)	26/32(81.2 %)	–	–	Not mentioned	–	5.4 %[b]	[b]
Xiaohong	2001–2004 China Prospective	523	523/523 (100 %)	39/523 (7.4 %)	7.1	Hepatic pedicle (100 %) Retro-pancreatic space (51 %) Common hepatic artery (100 %)	Not mentioned	32 (82.5 %)	0. 95 %[b] 19.6 %[a]	[b] [a]
Pooled data		5,844	51.6 % (19.7–83.5)[c]	44.5 % (27.4–61.7)[c]	6.4 (1.8–11.1)[c]	Common hepatic artery 91.9 % (88.9–94.9)[c] Hepatic pedicle 50.0 % (2.6–97.4)[c] Retro-pancreatic space 39.4 % (22.4–56.5)[c]		59.9 % (43.2–76.7)[c]	21.4 % (18.2–24.6)[c]	20.8 %(0-43.8)[c]

LND lymph node dissection, *LNM* lymph node metastasis, *TNLE* total number of lymph nodes examined, *TACE* transcatheter arterial chemoembolization, *RFA* radiofrequency ablation, *CI* confidence interval

[a] Post-operative

[b] Intraoperative

[c] 95 % CI

Table 2 Comparison of survival between patients with and without lymph node metastasis among hepatocellular carcinoma patients

Study	LNM			No LNM		
	N	Alive at 3 years	Alive at 5 years	*N*	Alive at 3 years	Alive at 5 years
Lee	25	3 (13.60 %)	3 (13.60 %)	2,009	1,085 (54 %)	763 (38 %)
Sun	49	16 (33 %)	13 (26 %)	919	570 (62 %)	431 (47 %)
Xiaohong	34	12 (37 %)	7 (22 %)	484	319 (66 %)	208 (43 %)
Pooled data	108	27.5 % (95 % CI 13.1–41.8)	20.8 % (95 % CI 13.2–28.4)	3,412	60.2 % (95 % CI 52.8–67.5)	42.6 % (95 % CI 36.6–48.6)

LNM lymph node metastasis, *CI* confidence interval

Discussion

The importance of LN sampling at the time of curative-intent surgical resection has been established for several gastrointestinal malignancies such as gastric,[86] pancreatic,[87] and gallbladder cancer.[88] Despite the strong negative prognostic effect of LNM in patients with HCC and ICC, the exact role of performing an LND has not been clearly established. Some authors suggest that an LND should be performed in all patients with primary liver cancer in order to appropriately stage individuals and guide perioperative management.[70,89] Conversely, other investigators studying the effects of LND have failed to find a prognostic effect of LN status on survival and thus have recommended against routine regional lymphadenectomy.[68] Unlike in patients with gallbladder cancer, a formal LND is not a part of the National Comprehensive Cancer Network (NCCN) guidelines for the treatment of HCC.[90] Furthermore, in patients with ICC, NCCN guidelines only suggest that an LND should be considered at the time of surgical resection. In this study, we pooled together individual patient data from previous reports of patients with HCC (n=5,844) and ICC (n=2,358) to generate one of the largest historical cohorts, in order to identify overall utilization of LND and the impact of LNM among these patients. We found that 51.6 % of patients with HCC and 78.5 % of patients with ICC underwent an LND in our cohort. Among these patients, we found that the presence of LNM with HCC or ICC conferred a worse overall survival compared with patients who did not have LNM.

After pooling individual patient data among studies analyzing the effects of LND and LNM in patients undergoing surgical resection for HCC, we found that despite the known negative prognostic significance of LNM, a formal LND was performed in only approximately one half (51.6 %) of patients. Among the patients who underwent a formal LND, 44.5 % of LND patients were found to have LNM. This incidence of LNM among patients with HCC is higher than those quoted in previous studies.[91,92] Previous reports of LNM among patients with HCC are quoted between 1 and 2 % among patients deemed to be candidates for surgical resection at the time of presentation.[93] Our meta-analysis, however, reveals a significantly higher incidence of LNM likely due, in part, to publication/selection bias as our new historical cohort included only studies in which LND was performed. Thus, the incidence of LND and LNM in the studies included in our historical cohort likely overestimates the "true" incidence of LNM generally found in patients with HCC. Specifically, selection bias is likely to have resulted in an overestimation in the rates of LND and LNM, as patients with suspected nodal involvement were more likely to undergo an LND. Our data do suggest, however, that among patients with HCC, those who do undergo LND—for whatever clinical indication—have a high incidence of LNM. Our data are similar to the findings by Sun et al.,[45] who reported that while only 5.1 % of all operable HCC patients had LNM, the incidence of LNM among patients undergoing LND was 81.2 %. Unfortunately, no randomized prospective trial has evaluated the incidence of LNM in patients undergoing LND for HCC. As such, current evidenced-based NCCN guidelines do not support a routine nodal dissection in patients with HCC.[90] However, several authors and institutions still support an LND at the time of HCC resection in order to adequately determine the extent of disease. Furthermore, previous authors have suggested a possible locoregional control benefit as support for performing an LND.[43] Despite this, as evidenced by our data, the exact method of LND is not standardized. In fact, though dissection along the common hepatic artery was performed in the majority of patients, only half of the patients received dissection of the hepatic pedicle. Regardless, the presence of LNM (3-year survival 27.5 %) conferred a worse prognosis compared with patients who did not have LNM (3-year survival 60.2 %). Supporting this, Lee et al.[57] found LNM to be an independent predictor for worse survival after controlling for various patient and disease-specific factors.

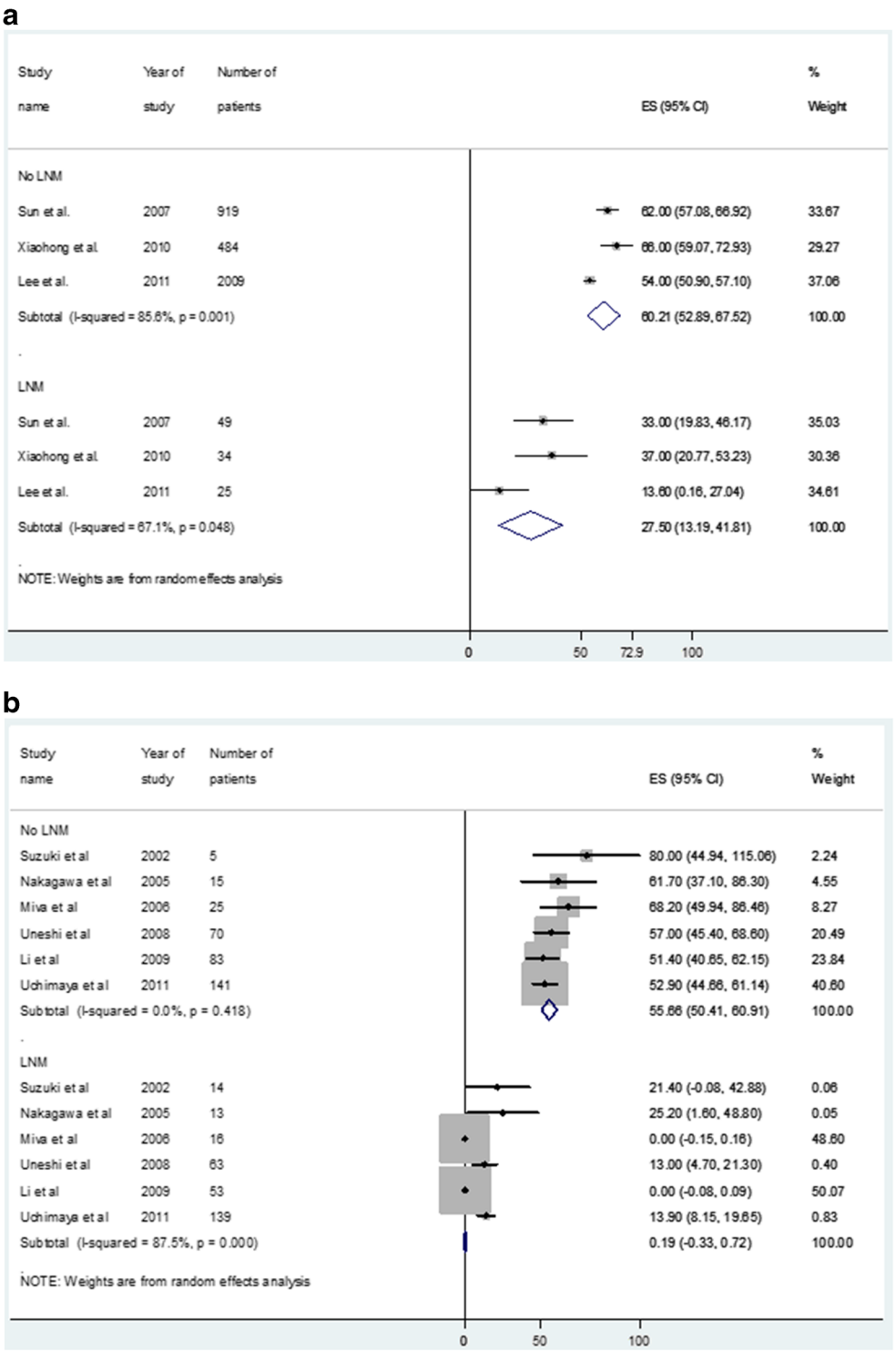

Fig. 2 Meta-analysis of 3-year survival among patients with **a** hepatocellular carcinoma (HCC) or **b** intrahepatic cholangiocarcinoma (ICC) stratified by lymph node status

As opposed to patients with HCC, NCCN guidelines suggest that surgeons should consider a formal regional LND for patients with ICC in order to provide relevant staging information.[90] Our data noted that the majority of patients with ICC did undergo an LND. In fact, over three quarters of the patients included in our analytic cohort (78.5 %) underwent an LND. Among these patients, 45.2 % were found to have LNM. Our data, however, consisted of pooled individual patient data largely derived from studies originating from Asian

Table 3 Study characteristic for patients with intrahepatic cholangiocarcinoma

Study name	Study characteristics	Number	Number of patients undergoing LND	Percent patients with LNM	Mean TNLE per patient	5-year survival after LND	Location of LND	AJCC stage	Recurrence of LNM
Ali	1997–2011 USA Retrospective	121	99/121 (82 %)	28/99 (28.2 %)	–	–	–	I, 36 % II, 16 % III, 8 % IVa, 40 %	–
Ercolani	1999–2001 Italy Prospective	10	10/10 (100 %)	4/10 (40 %)	6.8		Hepatic pedicle (25 %) Celiac trunk (25 %) Common hepatic artery (25 %)		5/10 (50 %)
Cho	2001–2007 Korea Retrospective	63	44/63 (69.8 %)	13/44 (29.5 %)	–	–	–		–
Choi	2000–2007 Korea Retrospective	51	30/51 (58.8 %)	15/30 (50 %)		–	Hepatoduodenal ligament (36 %) Common hepatic artery (32 %)	I, 32.8 % II, 31.2 % III, IV, 35.9 %	–
Guglielmi	1990–2012 Italy Retrospective	70	54/70 (77.1 %)	18/54 (34 %)	11.25	31.4 %	Hepatoduodenal ligament (62 %) Para-aortic area (10 %) Retro-pancreatic space (8 %) Common hepatic artery (6 %) Left gastric artery (6 %)	I, 15.7 % II, 28.6 % III, 7.1 % IV, 25.7 % Unknown, 22.9 %	–
De Jong	1973–2010 USA Retrospective	449	248/449 (55.2 %)	74/248 (29.8 %)	20.75	–	–		–
Li	1995–2005 China Retrospective	136	23/136 (17 %)	17/23 (73.9 %)	–	–	–	I, 11 % II, 35.3 % III, 26.4 % IV, 27.2 %	–
Miva	1989–2005 Japan Prospective	41	26/41 (63.4 %)	16/26 (61.5 %)	–	0 %	–		11/16 (68.7 %)
Murakami	1995–2010 Japan Retrospective	44	41/44 (93.1 %)	20/41 (48.7 %)	–	–	–	I, II, 38.6 % III, IV, 61.4 %	–
Nakagawa	1983–2004 Japan Prospective	44	30/44 (68.1 %)	13/30 (43 %)	–		–		–
Ribero	1990–2008 Italy Prospective	434	270/434 (62.2 %)	113/270 (41.8 %)	12.25	15.9 %	–	I, 15.9 % II, 24.7 % III, 1 % IV, 28.3 % Unknown, 30.2 %	–
Shimada	1990–2004	104	68/104 (65.3 %)	22/68 (32.3 %)	–	8 %	–		–

Table 3 (continued)

Study name	Study characteristics	Number	Number of patients undergoing LND	Percent patients with LNM	Mean TNLE per patient	5-year survival after LND	Location of LND	AJCC stage	Recurrence of LNM
	Japan Retrospective								
Shimada	1985–1999 Japan Prospective	44	41/44 (93 %)	24/41 (53.6 %)	–		–		–
Suzuki	1979–1998 Japan Retrospective	19	18/19 (94.7 %)	13/18 (72.2 %)	–	14.2 %		II, III, 31.7 % IV, 68.4 %	–
Tamandle	1997–2007 Austria Retrospective	69	46/69 (66.6 %)	18/46 (39 %)	11.75		Hepatoduodenal ligament (80 %) Coceliac (20 %)	I, 21.7 % II, 19.5 % III, 58.6 %	14/18 (77 %)
Tsuji	1980–1998 Japan Retrospective	39	39/39 (100 %)	24/39 (61.5 %)	30.75		Hepatoduodenal ligament (83 %) Common hepatic artery (50 %) Para-aortic area (46 %) Left gastric artery (25 %) Celiac trunk (20 %)		4/24 (16.6 %)
Uchimaya	1995–2004 Japan Retrospective	341	228/341 (66.8 %)	139/228 (60.9 %)	–	7 %	–		–
Uneshi	1985–2004 Japan Retrospective	133	133/133 (100 %)	63/133 (47.8 %)	–	10 %	Hepatoduodenal ligament (55 %) Common hepatic artery (42 %) Para-aortic area (17 %) Left gastric artery (14 %)	I, 4.5 % II, 18.7 % III, 38 % IV, 44.3 %	–
Yamamoto	1980–1996 Japan Prospective	70	51/70 (72.8 %)	23/51 (45 %)	–	0 %	Celiac artery (9 %) Hepatoduodenal ligament (82 %) Common hepatic artery (44 %) Retro-pancreatic space (35 %)		12/23 (52.1 %)
Yedibella	1995–2005 Germany Retrospective	45	18/45 (40 %)	6/18 (33 %)	6	0 %	Hilary lymphadenectomy (100 %) Celiac trunk (16 %)	I, II, 68.8 % III, IV, 31.2 %	
Yonemori	1998–2007 Japan Retrospective	31	31/31 (100 %)	12/31 (38.7 %)	11.8				–
Pooled data		2,358	78.5 % (76.2–80.7)[a]	45.2 % (39.2–51.2)[a]	13.8 (9.2–18.41)[a]	3.0 % (1.7–4.3)[a]	Hepatoduodenal ligament 44.5 % (37.9–51.1)[a] Common hepatic artery 9.5 % (6.5 %–12.5 %)[a]	I, 18.7 % (11.2–.26.1)[a] II, 24.2 % (19.2–29.2)[a] III, 22.4 % (9.1–35.8)[a] IV, 36.2 % (28.0–44.4)[a]	52.7 % (28.1–77.3)[a]

LND lymph node dissection, *LNM* lymph node metastasis, *TNLE* total number of lymph nodes examined, *AJCC* American Join Committee on Cancer, *CI* confidence interval

[a] 95 % CI

Table 4 Comparison of survival between patients with and without lymph node metastasis among patients with intrahepatic cholangiocarcinoma

Study	LNM			No LNM		
	N	Alive at 3 years	Alive at 5 years	*N*	Alive at 3 years	Alive at 5 years
Li	53	0 %	0 %	83	27 (51.4 %)	16 (30 %)
Miva	16	0 %	0 %	25	11 (68.2 %)	8 (48.9 %)
Nakagawa	13	4 (25.2 %)	–	15	8 (61.7 %)	–
Shimada	22	–	4 (8 %)	46	–	10 (45 %)
Uchimaya	139	20 (13.9 %)	10 (7 %)	141	73 (52.9 %)	65 (46.4 %)
Uneshi	63	9 (13 %)	7 (10 %)	70	34 (57 %)	30 (47 %)
Yamamoto	23	–	0 %	28	–	12 (51 %)
Suzuki	14	1 (21.4 %)	1 (14.2 %)	5	11 (80 %)	11 (80 %)
Pooled data	343	0.2 % (95 % CI 0–0.7)	0 %	413	55.6 % (95 % CI 50.4–60.9)	45.1 % (95 % CI 37.3–52.9)

LNM lymph node metastasis, *CI* confidence interval

countries (66 %) where LND is more commonly performed in patients with ICC. In a multi-institutional analysis,[34] de Jong et al. found an LND rate of only 55 % in Western centers treating ICC. In contrast, studies by Nakagawa et al.,[85] Choi et al.,[25] and Murakami et al.[77] reported that an LND is routinely performed at these East Asian institutions. Given the high rate of LNM found among patients undergoing LND in our cohort, the data strongly suggest the adoption of a routine LND for all patients with ICC. Again, however, the rates of LND and LNM are likely to be overestimated in these studies due to a combination of selection and publication bias. Despite this, our data shows that the presence of LNM confers a significantly worse prognosis among patients with ICC (3-year survival: LNM 0.2 % vs. no LNM 55.6 %). As such, a formal LND provides significant prognostic information that may help guide future perioperative management and surveillance. In addition to adequate staging, Guglielmi et al.[75] reported that overall survival was better among node-negative patients who underwent an LND versus those patients who did not. Taken together, a routine regional LND should be strongly considered in all patients undergoing surgical resection for ICC.

There are several limitations that should be considered when interpreting the data. The majority of studies included for analysis were retrospective in nature. Particularly in the case of LND rates, these studies may therefore suffer from selection bias. Furthermore, due to the paucity and heterogeneity of patient-level data, we were unable to control for other factors that may impact prognosis in addition to LNM such as extent of tumor invasion or presence of vascular invasion. Furthermore, most studies did not provide data on the extent of LND, thereby precluding any analysis of the anatomic area covered in any given "lymphadenectomy." The goal of this study, however, was to provide a comprehensive review of synthesized data on the utilization and impact of LND among patients with HCC or ICC. Finally, despite efforts to use the best statistical methods available to estimate aggregate means,[49] the TNLE reported may in fact be lower than estimated.

In conclusion, the performance of a regional LND in patients undergoing surgical resection for HCC and ICC was variable. Only approximately one half of patients with HCC and three quarters of patients with ICC underwent an LND at the time of surgical resection. Among those patients who did undergo LND, LNM was found in nearly one half of patients with HCC and ICC and conferred a significantly worse overall prognosis. While there are insufficient data to recommend a routine LND in all patients with HCC or ICC, given the potential valuable prognostic data that may help guide perioperative management, an LND should at least be considered. While the overall very low incidence of LND among patients with HCC makes routine LND perhaps unwarranted, the relative higher incidence of nodal metastasis among patients with ICC makes LND a stronger consideration for this disease. Further prospective studies are needed to determine the appropriate extent of LND and the impact of LND on perioperative morbidity among patients with primary liver cancer.

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