# Lymph node metastasis of intrahepatic cholangiocarcinoma: the present and prospect of detection and dissection

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Intrahepatic cholangiocarcinoma (ICC) ranks as the second most primary liver cancer that often goes unnoticed with a high mortality rate. Hepatectomy is the main treatment for ICC, but only 15% of patients are suitable for surgery. Despite advancements in therapeutic approaches, ICC has an unfavorable prognosis, largely due to lymph node metastasis (LNM) that is closely linked to the elevated recurrence rates. Consequently, the identification of precise and suitable techniques for the detection and staging of LNM assumes paramount importance for ICC therapy. While preoperative imaging plays a crucial role in ICC diagnosis, its efficacy in accurately diagnosing LNM remains unsatisfactory. The inclusion of lymph node dissection as part of the hepatectomy procedures is significant for the accurate pathological diagnosis of LNM, although it continues to be a topic of debate. The concept of sentinel lymph node in ICC has presented a novel and potentially valuable approach for diagnosing LNM. This review aims to explore the current state and prospects of LNM in ICC, offering a promising avenue for enhancing the clinical diagnosis and treatment of ICC to improve patient prognosis. Eur J Gastroenterol Hepatol 36: 1359–1369


## Introduction

Intrahepatic cholangiocarcinoma (ICC) is the most common type of primary liver cancer, second only to hepatocellular carcinoma [1,2]. The mortality rate of ICC is about 1–2/100 000 in most countries and is on the rise globally [3]. ICC may be related to chronic biliary inflammation caused by clonorchiasis, choledocholithiasis, cholelithiasis, or primary sclerosing cholangitis [4,5]. Besides, the research found a positive association of hepatitis B virus, hepatitis C virus, and Epstein–Barr virus infection in ICC with obvious genetic and clinicopathological characteristics [6,7]. Smoking, drinking, and nonalcoholic fatty liver disease are correlated with ICC [6]. ICC is a highly lethal carcinoma originating from bile duct epithelial cells of the intrahepatic biliary tree. Most ICCs are characterized by tubular or acinar adenocarcinoma with rich tumor stroma [8]. Clinically, ICC can be divided into intraductal growth, periductal infiltrating, mass forming, and the mixed patterns above [9]. Pathological subtypes of ICC are mainly divided into large-duct type and small-duct type [10]. The early symptoms of ICC are not obvious, and numerous patients are already in the advanced stage of ICC when diagnosed, which seriously affects the treatment. Hepatectomy is the main treatment for ICC [11], but only a small number of patients (15%) are suitable for surgery [12]. In addition, the 5-year survival rate after surgical resection is only 22–44% [5]. Although progress has been made to develop new treatment strategies, the prognosis of ICC is very poor [5]. The median survival time is only 7.0 months, and the 5-year overall survival (OS) rate is only 7.90% [13]. Postoperative recurrence and metastasis are the main causes of death in patients [14].

Lymph node metastasis (LNM) is the main metastasis of ICC. Tumor cells secrete proteases, such as matrix metalloproteinases, which degrade the surrounding stroma and basement membrane. Meanwhile, cancer cells release lymphangiogenic factors [e.g. vascular endothelial growth factor (VEGF)-C and VEGF-D], promoting lymphatic vessel formation around the tumor and providing a pathway for tumor cells to enter the lymphatic system [12]. Tumor staging, size, and the tumor microenvironment are all potentially related to LNM [15]. LNM plays a significant role in the poor prognosis and is strongly associated with a high recurrent rate in ICC [16]. In a multicenter study, the median OS of LNM is 18 months compared with 45 months of patients without LNM [17]. Imaging is an

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indispensable tool for diagnosing ICC and LNM. Methods of preoperative imaging to obtain LNM information include computed tomography (CT), MRI, and PET-CT. The accuracy of those methods to predict LNM is, however, not very satisfactory [18]. Performing the lymph node dissection (LND) during the hepatectomy in ICC is important for the precise pathological diagnosis of LNM but still remains controversial [19]. Some centers recognize LND as a procedure standard, while some surgeons only perform LND under certain circumstances [20]. The accurate guidelines and standards on LND of ICC are still under debate at present. Nowadays, sentinel lymph node biopsy (SLNB) is the standard procedure for treating melanoma and breast cancer [21,22]. Whether SLNB is suitable during ICC surgery still needs further research, but the concept of sentinel lymph node (SLN) seems to provide a new and potential method with inestimable value for LNM diagnosis.

In this review, the severity of LNM in ICC, the relationship between the primary tumor and the LNM, the accuracy of the preoperative imaging in LNM, the applicability of the LND, and the concept of SLN have been fully discussed. The summary of this article is shown in Fig. 1. Through the in-depth discussion, we hope to provide some insights into the diagnosis and treatment of LNM in ICC.

## Lymph node metastasis in intrahepatic cholangiocarcinoma: a poor prognostic factor of intrahepatic cholangiocarcinoma

The tumor microenvironment in ICC has an extensive lymphatic network, resulting in the rapid spread of ICC to regional lymph nodes (LNs) and liver parenchyma (Fig. 2) [23]. The liver, as the human body's largest lymphatic-producing organ with dense lymphatic channels [24], produces 25–50% of the body's lymph fluid [12]. With such a unique anatomical environment, lymphangiogenesis and lymphatic vessel hyperplasia are extremely common in ICC. Like angiogenesis in tumors, lymphangiogenesis could also lead to LNM and distant tumor metastasis [24]. High lymphatic vessel density is closely correlated with high-frequency recurrence and extensive LNM of ICC [25].

LNM occurs when cancer cells invade surrounding LNs and lymphatic vessels from the primary tumor and then spread to other parts of the body. ICC patients have a very high incidence of LNM. The incidence of LNM ranges from 17 to 62% [20]. Microscopic LN metastases have been demonstrated in more than 40% of ICC patients [11,20]. Roy *et al.* [12] summarized the molecular mechanism of LNM in detail. Lymphatic endothelial cells, carcinoma-associated fibroblasts, growth factors, and inflammatory chemokines are strongly associated with the development of lymphangiogenesis and LNM in ICC [12]. LN swelling, moderate or poor differentiation of tumor, serous pathological invasion, hilar and peripheral ductal infiltration, high serum carbohydrate antigen 19-9 (CA19-9) levels, and carcinoembryonic antigen (CEA) are significant risk factors and independent preoperative predictors for LNM in ICC [19,26]. Interestingly, tumor size does not appear to affect the occurrence of LNM [27,28]. Studies have shown that ICC patients presenting small tumors still exhibit a significant incidence of LNM [27]. In addition to the characteristics of the primary tumor,

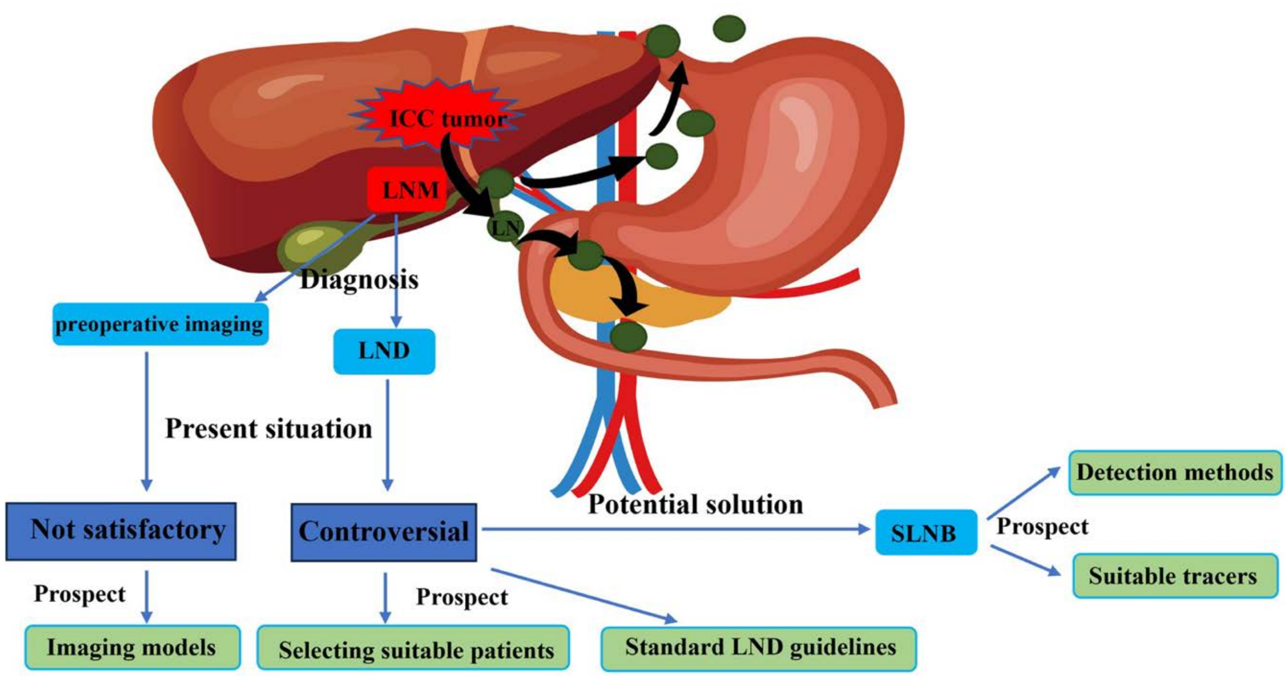
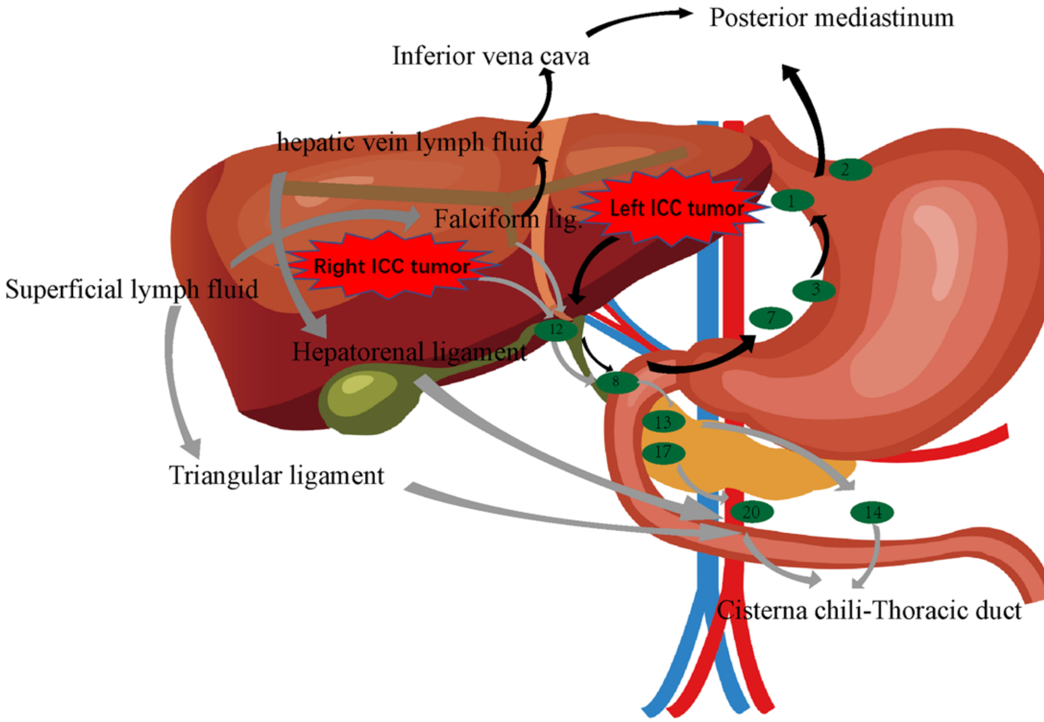



**Fig. 1.** Graphical abstract. LNM can be diagnosed by preoperative imaging and LND. The accuracy of the preoperative imaging, however, is not satisfactory, and imaging models need to be established. LND is a prerequisite for the pathological diagnosis of LNM, but LND is still under debate. We need to select suitable patients for LND and build the standard LND guidelines. SLNB is a potential way to solute the controversial LND with broad research prospects, the suitable detection methods and tracers to detect the SLNs need to be discovered and explored in the future. ICC, intrahepatic cholangiocarcinoma; LN, lymph node; LND, lymph node dissection; LNM, lymph node metastasis; SLNB, sentinel lymph node biopsy.




| Left ICC | | Right ICC | |
|---|---|---|---|
| 8 | the common hepatic artery LN | 8 | the common hepatic artery LN |
| 12 | the hepatoduodenal ligament LN | 12 | the hepatoduodenal ligament LN |
| 1 | the right paracardial LN | 13 | the superior mesenteric artery |
| 2 | the left paracardial LN | 14 | the LN in front of pancreas |
| 3 | the LN of lesser curvature of stomach | 17 | the paraaortic LN |
| 7 | the LN of left gastric artery | 20 | the posterior LN of head of pancreas |

**Fig. 2.** Hepatic lymphatic drainage and the high-incidence sites of LNM and the extent of LND resection. The black arrows indicate the left ICC lymphatic fluid and lymph node return, and the gray arrows indicate the right ICC tumor lymph node and lymph node return. Most of the liver lymphatic vessels retrograde flow along the Glissonean pedicle into the regional LNs. LNM is most likely to occur in the common hepatic artery LN (NO.8 LN) and the hepatoduodenal ligament LN (NO.12 LN), thus the NO.8 and NO.12 must be dissected during surgery. Right ICC should also dissect the right paracardial LN (NO.1 LN), the left paracardial LN (NO.2 LN), the LN of lesser curvature of stomach (NO.3 LN), and the LN of left gastric artery (NO.7 LN), while the left ICC should also dissect the superior mesenteric artery (NO.13 LN), the LN in front of pancreas (NO.14 LN), the paraaortic LN (NO.17 LN), and the posterior LN of head of pancreas (NO.20 LN). The lymph node classification and coding refer to the Japanese Society of Hepatobiliary and Pancreatic Surgery. ICC, intrahepatic cholangiocarcinoma; LN, lymph node; LND, lymph node dissection; LNM, lymph node metastasis.

the patient's health status also affects the risk of LND. For example, immunocompromised patients seem to be more susceptible to infection and tumor invasion, increasing the likelihood of LNM [29].

The location of LNM is related to hepatic lymphatic drainage and tumor location. The high-incidence sites of LNM are shown in Fig. 2. The nodal stations are described according to the Japanese Society of Hepato-Biliary-Pancreatic Surgery [30]. LNM tends to occur in the hilar, hepatoduodenal ligament, peripancreatic, and common hepatic artery LNs in ICC patients, and the left ICC simultaneously tends to spread to the celiac and gastro-cardiac LNs while the right ICC rarely spreads to these areas [31,32]. According to the 8th American Joint Committee on Cancer (AJCC) guidelines, the regional LN group of the right ICC includes the periduodenal, hilar, and peripancreatic LNs, and the regional LN group of the left ICC includes the hilar, gastrohepatic, and inferior phrenic LNs [33]. Most of the liver lymphatic vessels retrograde flow along the Glissonean pedicle and drain along the hepatoduodenal ligament into the regional LNs [20], thus the hepatoduodenal ligament LN (the No. 12 LN) is the most common site of LNM in ICC [34,35], and the second is the common hepatic artery LN (the No. 8 LN) [35]. The incidence of LNM in hilar ICC and tumors near the second level of confluence is much higher than that in peripheral ICC [36,37]. Clinicopathologic analysis showed that LNM occurs more frequently in the hilar type than the peripheral type (51.6% vs. 13.6%) in ICC [38]. Large-duct type ICC has a higher risk (42.9% vs. 5.4%) of developing LNM than small-duct type ICC [39]. Clinical features of large-duct and small-duct types are similar to those of hilar and peripheral ICC respectively, but these are not entirely the same. The ductal types are divided based on histopathology, not location. The cells of the large-duct type are tall and columnar, forming large glands that secrete mucus, mainly distributed around the hilar of the liver. The cells of the small-duct type are cuboidal, forming smaller glands and have no mucus, mainly distributed around the peripheral liver.

LNM is thought to be partially responsible for the progression and spread of ICC, seriously affecting patients' survival rate and quality of life with extremely poor prognosis and huge economic burden [40]. Research on LNM and the prognosis in ICC are summarized in Table 1. Multivariate analysis indicated that LNMs are one of the strongest independent poor prognostic factors for ICC [17,44,41]. Systematic review analysis shows that the 3-year survival rate of LNM patients is 0.2%, and the 5-year survival rate is almost 0%, while the 3- and 5-year survival rates of non-LNM patients are 55.6% and 45.1% [40]. Survival analysis revealed a strong association between the number of metastatic LNs and poor prognosis in ICC [16,35]. The more the LNMs, the worse the median OS in ICC patients (no LNM 45.0 months vs. 1–2 LNMs 19.8 months vs. more than 3 LNMs 16.0 months) [17]. Compared with patients without LNM, the risk of death in patients with LNM is increased by more than 3 times [42,45]. Comprehensively investigating the risk factors for LNM is critical for the diagnosis, treatment, and prognostic assessment of ICC patients. Early and effective diagnosis and treatment are the key to reducing the risk of LNM and improving survival rates.

## The preoperative imaging of lymph node metastasis in intrahepatic cholangiocarcinoma: the accuracy is not satisfied

Given the strong association of LNM with ICC prognosis, it is extremely crucial to obtain information on whether a patient has LNM or not. Preoperative assessment of the status of LNM has become a paramount issue for accurate intraoperative excision [18]. The radiology-based method could predict the LNMs of ICC, which is helpful for preoperative surgical decisions [46,47]. The accuracy of the preoperative imaging methods (CT, MRI, and PET-CT) to predict LNM, however, is not satisfied [18]. Inaccurate preoperative imaging may miss pathological LNM and impair the therapeutic value of LND [48]. Multicenter studies showed that the radiographic LNM staging was inaccurate in up to 34.2–40% of ICC patients [45,49]. Among those methods, CT is the most commonly used preoperative imaging for diagnosis and preoperative evaluation in ICC. Although the preoperative CT features are significantly different between ICC patients with and without LNM [50], CT has limited value in predicting regional LNM of ICC [51]. Its sensitivity is only 30–50%, which is quite low [47]. MRI as a key preoperative imaging of ICC hepatectomy showed limited specificity (56.7–64.3%), sensitivity (53.2–57.1%), and poor positive predictive value (48.0–58.1%) for LNM diagnosis of ICC [52,53]. A multicenter retrospective investigation conducted by Ke *et al*. [54] showed that the incidence of LNM in patients with clinically node-negative on preoperative imaging after LND was still as high as 40.6%, suggesting that preoperative CT and MRI have limited value in diagnosing LND. PET-CT is the most accurate imaging method for diagnosing malignant tumors, it has significantly higher accuracy in diagnosing regional LNM and distant metastasis in ICC patients compared with CT and MRI [55]. Although its specificity is reliable in diagnosing LNM in ICC (96.1–100%), its low sensitivity (31.2–43%) [56,57] and the high cost, however, greatly limit its clinical application.

Some preoperative assessment models have been built to improve the accuracy of preoperative imaging. For example, Ji *et al*. [47] applied CT radiomics to preoperatively predict LND and found that the area under the curve in the validation cohort of the radiomics nomogram reached 0.89, which exhibits good predictive ability and distinguishing characteristics. Huang *et al*. [26] combined the imaging changes with serological indicators (CA19-9, CEA, aspartate aminotransferase) to help determine the status of the patients' LNs more precisely (specificity: 70–90%; sensitivity: 82–86%). Xu *et al*. [18] built a support vector machine model, and the LNM status could be staged more accurately (specificity: 60.98%; sensitivity: 87.88%) by combining the support vector machine score, CA19-9 level, and LNM factors reported by MRI. Holzapfel *et al*. [58] showed that diffusion-weighted

**Table 1.** The summary of research on lymph node metastasis and the prognosis in intrahepatic cholangiocarcinoma

| Researchers | Types of study | Total cases | Cases of LND | LNM | Prognosis | Findings and significance |
|---|---|---|---|---|---|---|
| Umeda *et al*. [20] | Multicenter Study | 310 | 224 (72%) | 90 (40%) | Median survival: ：N+ 16.9 months vs. N0 57.2 months | The specific positioning of LNM is comprehensively elaborated. |
| Ruzzenente *et al*. [27] | Multi-institutional cohort study | 259 | 194 (74.9%) | 72 (37.1%) | 5-year OS: small ICC, N0 84.8% vs. N+ 36.0%; large ICC, N0 45.7% vs. N+ 12.1% | LNM incidence is independent of tumor size. |
| de Jong *et al*. [28] | Multi-institutional cohort study | 449 | 248 (55%) | 74 (30%) | Median survival: N+ 24 months vs. N0 30 months | LNM, vascular invasion, and tumor number are strongly associated with prognosis. |
| Chen *et al*. [41] | Population-based study | 664 | 331 (51.4%) | 103 (31.1%) | Median CSS: N+ 19.0 months vs. N0 54.0 months | (1) LNM is a pivotal independent prognostic factor for ICC.<br>(2) Four or more LNs may be sufficient for appropriate ICC staging. |
| Zhang *et al*. [17] | Multicenter Study | 1036 | 603 (54.7%) | 249 (41.3%) | Median OS: N+ 18.0 months vs. N0 45.0 months | (1) Proposed a new nodal staging of N0, N1 (1–2 LNMs), N2 (more than 3 LNMs).<br>(2) Assessment of 6 or more regional LNs allows optimal staging of ICC. |
| Bagante *et al*. [42] | Multi-institutional cohort study | 561 | 272 (48.5%) | 123 (45.2%) | 5-year DSS: N0 28.1% vs. 1–3 LNM 10% vs. 3 or more LNM 0% | (1) LNM is one of the strongest poor prognostic predictors in ICC.<br>(2) Routine LND should be considered during resection to obtain accurate staging of ICC. |
| Jutric *et al*. [43] | Data review | 849 | 492 (58.0%) | 160 (32.5%) | Median survival: N+ 15 months vs. N0 37 months | (1) OS of LNM in ICC patients is poor.<br>(2) Strong consideration for routine LND. |

CSS, cancer-specific survival; DSS, disease-specific survival; ICC, intrahepatic cholangiocarcinoma; LN, lymph node; LND, lymph node dissection; LNM, lymph node metastasis; OS, overall survival.

imaging combined with a respiratory-triggered single-shot echo-planar imaging sequence is another promising imaging modality with high accuracy (specificity: 92.8%; sensitivity: 83.3%) for LNM predictions, but the measurement in small LNs still seemed to be unreliable. Zhu *et al.* [50] developed a nomogram based on the different features in CT to predict LNM with a specificity of 86.8% and a sensitivity of 68.0%.

Preoperative imaging and novel risk prediction models can indeed provide plenty of basic information such as the internal structure of the tumor, the size and shape of LN, the presence of adjacent and distant invasion, and LNM-related molecules, demonstrating certain LNM prediction and screening capabilities [18,58]. No matter how these models are established, it is still, however, impossible to achieve a definite diagnosis of LNM in ICC. The immune response to nontumor antigens in draining LNs may result in inflammatory hyperplasia of the nodes. Therefore, swollen LNs do not always possess metastases, which can be evaluated accurately only by microscopic diagnosis. Besides, due to the minor nodal metastasis, tumor heterogeneity, T stage, or other indicators are still unable to accurately furnish and predict key clues such as nodal status and the number of nodal metastases, which are not necessarily applicable to the complex, multidimensional, and variable nonlinear situations of LNM clinically. Those methods should not be considered as valid alternatives for LND [59].

## Lymph node dissection in intrahepatic cholangiocarcinoma: can obtain accurate staging of lymph node metastasis but under debate

LND is a prerequisite for pathological diagnosis of LNM and promises to contribute more indispensable evidence such as LNM status, location, and number [54]. In addition, LND can also eliminate potential micrometastatic lesions to directly reduce the recurrence and metastasis rates to some extent [60]. The role of LND is for accurate staging as well as the resection of occult LNM to reduce the risk of recurrence and achieve a better prognosis. In the 8$^{th}$ definition of AJCC, LND is described as dissecting more than six LNs during surgery, including LNs along the common hepatic artery, behind the head of the pancreas, around the hepatoduodenal ligament, and around the left gastric artery [31]. For the right ICC, the periduodenal LNs, peripancreatic LNs, and hilar LNs should be dissected, while for the left ICC, the gastrohepatic LNs and subphrenic LNs should be dissected [32]. The No.12 and No.8 LNs must be included during the LND for accurate staging [32].

Whether LND can be exploited as a routine intraoperative resection and whether LND is beneficial for patients without LNMs are currently debated. Previous studies that had a favor on LND are shown in Table 2. Some research showed that under similar tumor characteristics and background, the OS (LND− to LND+: 44 months to 90 months) was significantly prolonged after LND [31,61]. The survival rate of patients with three or more LNs resected is remarkably higher than those of patients with only 1–2 LNs resected (3-year cancer-specific survival rate: 1–2 dissection to 3–6 dissection: 10.8 months to 35.3 months) [62]. For LNM patients, surgical resection of more than four LNs can notably obtain long-term oncological outcomes [35]. After propensity score matching, to reduce the influence of other prognostic factors, was employed, LND improves the oncology outcomes, and adequate LND significantly improves the tumor prognosis of ICC during radical surgery [20,31]. Besides, LND provides critical information on LN status to enable accurate staging of ICC, which affects and guides the follow-up further treatment, postoperative monitoring, and the choice of adjuvant therapy [17,40,41,54]. Ruzzenente *et al.* [27] found no significant difference in the occurrence of LNM between the small ICC and large ICC, indicating that LND should be mandatory during

**Table 2.** The clinical value of favoring lymph node dissection on the prognosis and staging

| Researchers | Study types | Total cases | LND | Resected LNs | Prognosis | Opinions on LND |
|---|---|---|---|---|---|---|
| Bagante *et al*. [45] | Multicenter study | 1154 | 515 (44.6%) | Median HLNs: 4<br>≥6 HLN: 217 (42.1%)<br><6 HLN: 298 (57.8%) | 5-year OS: N0 with ≥6 HLNs 54.9% vs. with <6 HLNs 39.4% ($P$ = 0.098); N1 with ≥6 HLNs 17.9% vs. with <6 HLNs 12.5% ($P$ = 0.72); Nx: 44.0% | (1) Only 1/4 of patients could meet the AJCC nodal staging standard.<br>(2) 6 HLN cutoffs are associated with prognosis in N0 patients but not N1 patients. |
| Ke *et al*. [54] | Multicenter study | 380 | 106 (27.9%) | Median HLNs: 3.5 (1–39) | Median OS before matching: LND+ 24.0 vs. LND− 18.0 months ($P$ = 0.30)<br>Median OS after matching: LND+ 24.0 vs. LND− 14.0 months ($P$ = 0.02) | (1) LND benefits selected LNM-negative ICC patients.<br>(2) LND is an independent risk factor for OS. |
| Kim *et al*. [31] | Propensity score-matched study | 148 | 73 (49.3%) | Median HLNs:12 (8–18) | DFS: LND− 20.0 months vs. LND+ 64.0 months ($P$ = 0.077); OS: LND− 44.0 months vs. LND+ 90.0 months ($P$ = 0.027) | (1) LND could improve oncologic outcomes and benefit ICC patients.<br>(2) Well-designed prospective studies are needed to further elucidate the role of LND. |
| Chen *et al*. [61] | Multicenter study | 563 (LNM+ is excluded) | 261 (46.3%) | Median HLNs: 6 (2–8) | After matching, OS: LND− 8.0 vs. LND+ 23.0 months ($P$ < 0.001); RFS: LND− 15.0 vs. LND+ 13.0 months ($P$ = 0.029) | (1) The optimal number of HLNs is more than 8.<br>(2) Routine LND in LNM-negative ICC patients is beneficial for accurate staging and better prognosis. |
| Umeda *et al*. [20] | Multicenter study | 310 | 224 | Not mentioned. | After matching, LND+ group had better 1-, 3-, and 5-year OS (83.5%, 52.2%, and 42.8%) than LND− group (71.9%, 32.4%, and 23.4%, $P$ = 0.046). | LND plays a significant role in improving oncologic outcomes. |

DFS, disease-free survival; HLN, harvested lymph nodes; LN, lymph node; LND, lymph node dissection; LNM, lymph node metastasis; OS, overall survival; RFS, relapse-free survival.

hepatectomy regardless of tumor size. In addition, LND prevents potential micrometastatic lesions and missed diagnosis due to inaccurate preoperative evaluation and reduces locoregional recurrence since LN is the most common recurrence site of ICC [63]. Sposito *et al.* [64] indicated that LND contributes to a marked survival benefit for clinically LNM-negative patients, and the benefits of LND for early-stage tumors and healthy livers are significant. LND facilitates more precise pathological staging, guiding more adaptive treatment and closer postoperative monitoring. Therefore, lots of scientists suggest that routine LND should be considered during resection to obtain accurate ICC staging [42].

Routine LND, however, is not recommended by some institutions, especially in Western centers [40,45]. Previous studies that oppose LND are shown in Table 3. Some research showed that the OS was not overtly improved after LND regardless of LN status [34,44,65, 66, 69, 70]. For LNM-negative patients, Li *et al.* indicated that only 4.9% of patients without LNM benefited from preventive LND to prevent possible microscopic LNMs and clearance of metastases, and preventive LND does not bring any survival benefit (LND+ vs. LND−: 3-year OS: 26% vs. 31%; 5-year OS: 15% vs. 17%, $P = 0.822$) [34]. In their view, LNM is a systemic disease, not just a LN lesion. Patients with regional LNM are also likely to have distant LNM since some lymphatic outflow channels are directly connected to distant areas of the total lymphatic system [71]. In addition, due to the complex lymphatic drainage network of the liver, we cannot systematically dissect all the LNs around the liver. The current so-called systematic LND may only be LN sampling when ICC is associated with LNM. Using LND to dissect metastatic LNs is not enough to achieve the therapeutic effect, nor does it contribute to the oncology results [37]. In addition, LND increases surgical trauma, prolongs surgical time, increases bleeding volume, and increases surgical difficulty and risk. The postoperative complications (such as more tissue damage, lymphatic fistula, bile leakage, intestinal obstruction, and infection) in LND+ group are significantly higher [66]. The increase in postoperative complications after LND is related to the higher risk of disease-specific death [66]. The incidence of complications of LND in patients with cirrhosis is as high as 71%, severely limiting the role of LND in specific cases [11].

LND is not suitable for all surgical patients. More than 80% of LNDs turn out to be unnecessary [72]. After understanding all the benefits and risks of LND, we need to establish a set of criteria to evaluate which patients are suitable for LND before surgery. Some institutions indicated that LND should be recommended for intermediate and high-risk patients with LNM, but not for low-risk patients [34]. The National Comprehensive Cancer Network (NCCN) clinical practice guidelines indicate that local lymphadenectomy should be considered only in highly selected cases in ICC [73]. According to the NCCN, LND resection should be prohibited for patients with extrahepatic LNM and distant metastatic diseases [73]. For patients with major vascular invasion, CEA > 5.0, and LNM outside the hepatoduodenal ligament, the survival benefit of LND is poor [62]. Umeda *et al.* [20] also pointed out that whether LND applies to the patients depends on the localization of the tumor. Hilar ICC showed significant therapeutic value from LND, whereas LND had no therapeutic benefits for peripheral ICC [20]. LN biopsy, however, is recommended for all patients with ICC for accurate staging [64]. Accurate nodal staging can help guide pathologic staging and further guide postoperative adjuvant therapy. For patients with LNM assessed on preoperative imaging, LND is required to reduce local recurrence. For ICC patients with no LN swelling as assessed by preoperative imaging, prophylactic LND is also recommended by some institutions to accurately assess LN

**Table 3.** The clinical value of not favoring lymph node dissection on the prognosis and staging

| Researchers | Study types | Total cases | LND | Resected LNs | Prognosis | Opinions on LND |
|---|---|---|---|---|---|---|
| Kim *et al*. [65] | Multi-institutional study | 215 | 102 (47.4%) | Mean HLNs: 12.8 ± 8.0 (range 4–51) | DFS: no difference between LND+ and LND− groups ($P = 0.111$); recurrence rates: LND+ 73.5% vs. 64.7% LND− group. | (1) No survival benefit of LND has been shown in ICC. (2) LND is useful for ICC staging. |
| Li *et al*. [34] | Multicenter study | 124 | 53 (42.7%) | Median HLNs: 6 (1–16) | 1-, 3-, and 5-year OS: LND+ 69%, 26%, and 15% vs. LND− 64%, 31%, and 17% ($P = 0.822$) | No survival benefit of LND has been shown in ICC and routine LND is not recommended. |
| Zhou *et al*. [66] | Systematic review | 1377 | Not mentioned | Not mentioned. | No difference between LND+ and LND− groups in OS (HR: 1.13, $P = 0.20$), DFS (HR: 1.23, $P = 0.13$), or recurrence (OR: 1.39, $P = 0.14$). | The prognosis after LND was not significantly improved after LND regardless of LN status. |
| Yeow *et al*. [67] | Systematic review | 3776 | 2087 | Not mentioned. | No difference between LND+ and LND− groups in OS (HR: 0.78, $P = 0.11$), DFS (HR: 0.84, $P = 0.07$) and complications ($P = 0.75$) | (1) LND does not bring survival benefits to patients overall. (2) LND achieves better OS and RFS for cN0 patients. |
| Kizy *et al*. [68] | Retrospective cohort study | 169 | 148 (88%) | Not mentioned. | No difference between LND+ and LND− groups in median survival [19 months 95% Confidence Interval (CI) 17–33 vs. 20 months CI 10–27, $P = 0.323$] | LND for patients with LN-positive ICC may not bring survival benefits compared to chemotherapy alone. |
| Chen *et al*. [41] | Retrospective cohort study | 664 | 331 (51.4%) | Not mentioned. | No difference between LND+ and LND− groups (5-year CSS 13.1% vs. 44.9%, $P < 0.001$) | (1) No survival benefit of LND has been shown in ICC. (2) LND is useful for ICC staging. |

CSS, cancer-specific survival; DFS, disease-free survival; HLN, harvested lymph nodes; HR, hazard ratio; LN, lymph node; LND, lymph node dissection; LNM, lymph node metastasis; OR, odds ratio; OS, overall survival; RFS, relapse-free survival.

status and reduce local recurrence [71], although the LND procedure may not provide any clinical benefit.

Furthermore, for patients undergoing LND, we also need to establish a standard set of LND guidelines. Currently, there is no authoritative standard for the definite scope of LND and usually depends on the provisions of institutions or the experience of the surgeon. Surgical approaches to LND vary with significant differences [48]. Eighth edition AJCC guidelines and multicenter study indicated that at least six LNs should be evaluated after operation to accurately judge ICC staging [17,74]. Research, however, showed that only a few (22.1–27.5%) patients could meet this standard and get full evaluation [42,45]. The median number of LNs collected in the numerous research was 4 [45,54,62]. Four LNs could be sufficient to obtain accurate staging [41], but the multicenter study showed that assessment of six or more regional LNs allows the optimal staging of ICC [17]. Appropriate additional LND on the basis of six LNs may be able to further reduce the risk of missing LN that may have metastasized. In short, a standard set of LND guidelines needs to be established to help doctors achieve accurate staging without missing any potentially metastatic LN.

## Sentinel lymph node biopsy (SLNB) in intrahepatic cholangiocarcinoma: a perspective solution

As discussed earlier, debate continues about the applications of LND in ICC [19]. On the one hand, no-LND may lead to the omission of LNM and inaccurate staging of ICC. On the other hand, performing LND also carries a high risk of postoperative complications and uncertain oncologic outcomes [66]. In addition, the radioactive LN staging and imaging modality of ICC still have a high rate of missed detection and inaccuracy (40% of ICC patients are inaccurate) [45]. False negative and false positive cases in imaging are often encountered. To achieve accurate staging and eliminate the negative impact of LND, the SLNB may provide us with a potential solution [75].

SLNs refer to the first batch of LNs that receive the lymph flow from the primary tumor, which is the first place that cancer cells accumulate and develop LNM [76]. SLNB has been used clinically to perform the minimally invasive surgery in various cancers such as melanoma, breast cancer cervical cancer, gastric cancer, and endometrial cancer [21,22,77,78]. SLNB can provide accurate LN status during operation, minimizing the scope of surgery and avoiding postoperative complications caused by unnecessary LND such as infection, tissue damage, lymphatic fistula, and postoperative edema. Additionally, it can reduce the operation time [79]. Since no imaging modality could accurately detect LNMs in the early cancer stage, SLNB provides a highly reliable method to screen LNMs, including micrometastases [21]. Few research, however, has been done on the SLN in ICC. Due to the complexity of the liver lymphatic system and the difficulty of surface or endoscopic examination, using standard radioisotope methods that require injection of tracers to map the SLNs in ICC is considerably challenging [80].

First of all, we must confirm whether the liver has SLNs or not. In preclinical studies, using dual near-infrared fluorophores and indocyanine green (ICG), Wada *et al.* [79] proved the presence of SLN in the liver of the swine model, indicating that the concept of SLN applies to the liver. Besides, the combination use of dual near-infrared fluorescence imaging enables real-time identification between regional LNs and SLNs [79]. Mihara *et al.* [80] also indicated that by using dual-tracer superparamagnetic iron oxide nanoparticle (SPIO) and ICG, the detection of SLNs in situ is feasible in the ICC swine model. This double tracer method can detect almost all SLNs of intra-abdominal organs by laparoscopic approach [80]. Since the swine liver is a suitable model for measuring lymphatic flow whose anatomy and size are similar to that of humans, these conclusions and methods may also be applicable to humans.

Second, we need to develop appropriate tracers and detection methods to detect SLN in ICC. Due to the complex lymphatic system of the liver, each individual has individual differences in lymphatic reflux, and the SLNs of the liver are not in a fixed position compared to the breast. The unpredictability and variability of hepatic lymphatic drainage greatly increase the detection difficulty [72]. Kurochkin *et al.* [76] summarized the promising photonic tools used for SLN exploration, including fluorescence imaging, photo-switching dyes, MRI detection, and combined photoacoustic imaging. Further clinical research, however, is urgently needed to confirm the validity and feasibility of these methods in ICC.

ICG is instrumental in determining the range of LND and represents a promising tool for detecting SLN in ICC patients. ICG fluorescence has been widely researched in multiple cancer types to detect SLNs [81,82]. ICG has been proven to be an excellent SLN tracer, superior to methylene blue and radioisotopes [83]. ICG imaging has been preliminarily studied for its clinical application in laparoscopic LND of ICC, and intraoperative ICG staining has been corroborated to guide the dissection of draining lymphatic vessels and LNs, determining the regional lymphatic drainage pattern in ICC [48]. Wang *et al.* [84] established a set of consensus guidelines for the use of ICG fluorescence imaging during hepatobiliary surgery. ICG tumor imaging in ICC can be administered nonintravenously or intravenously according to the consensus. For tracking LN patterns in ICC, intraoperative laparoscopic injection of ICG under the hepatic capsule is a suitable method [48]. Zhang *et al.* [48] performed laparoscopic injection under the corresponding liver capsule with the ICG solution of 0.025 mg/ml, and the injection angle was controlled to 10–15 degrees with the liver to prevent ICG from entering the liver parenchyma and staining failure. The dosage of ICG is not the same for different purposes (e.g. tumor imaging: 0.5 mg ICG/kg body weight before surgery; anatomic resection-positive staining: 0.05–0.025 mg ICG/ml aqueous solution with 5 ml before surgery) [84]. Due to the small tracer of ICG, ICG, however, would show an escape from SLN to the second layer nodes [80]. The small amount of accumulation and the short residence time in LNs of ICG [85] make the quantitative analysis of SLNs difficult [80].

Newly designed nanoparticles are very attractive for SLN localization. Ultra-sensitive and highly specific nanoparticles provide a novel method to detect tumor SLN due to their strong tumor-targeting affinity and specificity, excellent biocompatibility, low toxicity, and self-luminescence [85]. Magnetic nanoparticle tracers such as SPIOs are promising SLN tracers [86], which have been studied in detecting SLNs in clinical breast cancer and preclinical gallbladder cancer [86]. Mihara *et al.* [80] injected the SPIO into the gallbladder wall of the swine gallbladder cancer model during surgery, and LNs containing SPIO nanoparticles were identified by the laparoscopic magnetic probe with a magnetic field count of 2.5–15.9 μT. Carbon nanoparticle suspension has been clinically proven with a high SLN detection rate and clinical diagnostic validity in early-stage cervical cancer and breast cancer [87,88], which is another promising SLN tracer but needs further study in the field of ICC. Given the limited research in this area, these methods may also have broad research prospects in the SLN of ICC. Once proven clinically beneficial, it will greatly advance the diagnosis and treatment of ICC.

## Lymph node metastasis and intrahepatic cholangiocarcinoma: biomarkers and molecular driving mechanism

In addition to CA19-9 and CEA that are two classic biomarkers of LNM in ICC [89], various suitable and novel biomarkers have been developed to evaluate the LNM in ICC and predict the prognosis. D-dimer combined with preoperative CA19-9 has been proven to be an effective biomarker to predict LNM and prognosis after curative resection in ICC patients [90]. Serum angiopoietin-like protein 4 is a novel discovered prognostic biomarker. Compared with CA19-9 and CEA, it has a superior predictive rate and efficiency in LNM and vascular invasion of ICC patients [91]. Interleukin-35 is a newly discovered cytokine produced by regulatory T cells, which is found to be overexpressed in ICC tissues, and positively correlated with LNM and vascular invasion [92]. As well as its receptor gp130, those two are independent prognostic factors of ICC patients [92]. VEGF plays a significant role in the process of LNM and suppressive immune microenvironment in ICC. Meta-analysis indicated that the high expression of VEGF in ICC tissues is closely associated with the LNM as well as the advanced tumor node metastasis stage [93]. Overexpression of free fatty acid receptor 4 is intimately linked to the process of epithelial-mesenchymal transition, and it has been proved to be strongly related to the LNM and poor prognosis of ICC, thus acts as a promising novel diagnostic biomarker and therapeutic target [94].

Tumor lymphangiogenesis plays a key role in the development of LNM, but current drug therapy mainly focuses on antiangiogenesis [95]. Drugs targeting lymphangiogenesis still need further research. VEGF-C and VEGF receptor 3 (VEGFR3) signaling is a critical pathway for the formation of lymphatic vessels. Various potential drugs targeting this signaling pathway have been developed to inhibit tumor lymphangiogenesis, thereby suppressing LNM [96]. Monoclonal antibodies (e.g. bevacizumab and VGX-100) and decoy receptors (e.g. VEGFR3eIgG) are part of the VEGFR3 inhibition-based therapies [12]. For other signaling pathways targeting the LNM, Sheng *et al.* [97] found that ephrin type-A receptor 2 (EPHA2) is frequently mutated in ICC. EPHA2 may promote the LNM through the Notch-1 signal pathway, thus inhibiting EPHA2 mutations could effectively inhibit the occurrence of LNM [97]. Yang *et al.* [98] found that eukaryotic translation initiation factor 5A2 could promote LNM and bile duct invasion through phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin signaling pathway. Zhang *et al.* [99] found that S100 calcium-binding protein A11, a member of the S100 family, could promote tumor proliferation and LNM through P38/mitogen-activated protein kinase signaling pathway. Carpino *et al.* [23] found that the proteins thrombospondin 1, proteins thrombospondin 2, and pigment epithelium-derived factors could inhibit vascular growth and promote lymphangiogenesis in the tumor microenvironment of ICC. The potential therapeutic drugs developed against these targets and signal pathways may prevent and treat the LNM in ICC with broad research prospects.

## Concluding remarks

LNM serves as an independent and critical poor prognostic factor of ICC, yet the accuracy of its imaging diagnosis remains inadequate. LND as a prerequisite for pathological diagnosis of LNM, its pros and cons, and the controversial points were fully discussed. At least 4–6 LNs should be evaluated during operation to accurately judge ICC staging. Not all patients are suitable for LND, and we also need to establish a standard set of LND guidelines for ICC patients. The discovery of the occurrence of SLN in ICC is exciting, which provides us with a potential solution to the LNM in ICC. The clinical applicability of SLNB in ICC requires validation, as it has the potential to significantly enhance the level of clinical diagnosis and treatment for ICC. The detection and dissecting LNM in ICC has been extensively discussed in this review, hoping to open up a new way to improve the clinical diagnosis and treatment of ICC.

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### *Conflicts of interests*

There are no conflicts of interest.

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