Review Article

Extrahepatic Lymphadenectomy in Intrahepatic Cholangiocarcinoma: Current Evidence and Controversies

Linfadenectomia Extra-Hepática no Colangiocarcinoma Intra-Hepático: Evidência Atual e Controvérsias

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ABSTRACT

Lymph node metastasis (LNM) is one of the most adverse prognostic factors in intrahepatic cholangiocarcinoma (iCCA), with five-year overall survival rarely exceeding 15% in node-positive patients. The role and extent of extrahepatic lymphadenectomy in this setting, however, remain controversial. This narrative review synthesizes the current evidence on nodal assessment in iCCA, including prognostic implications of nodal disease, preoperative prediction of LNM, survival benefit of lymphadenectomy, and postoperative morbidity. Prognosis is particularly poor in patients with multiple positive nodes, high lymph node ratio, or metastases beyond the hepatoduodenal ligament. Preoperative imaging with computed tomography (CT) or magnetic resonance imaging (MRI) has limited accuracy for nodal staging, while PET-CT and endoscopic ultrasound with fine-needle aspiration provide improved detection in selected cases. To address this limitation, predictive nomograms have been proposed, which integrate clinical, biochemical, and radiological variables and are available as online calculators for daily practice. From a surgical perspective, adequate lymphadenectomy, defined by retrieval of at least six lymph nodes, remains essential for accurate staging and should be tailored to tumor laterality, involving stations 1, 3, 7, 8, and 12 for left-lobe tumors and stations 8, 12, and 13 for right-lobe tumors. Although its therapeutic role is still debated, a growing number of studies published in recent years suggest that lymphadenectomy

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may confer a survival benefit, particularly in clinically node-negative patients undergoing R0 resection and in those with less aggressive tumor biology.

Keywords: Cholangiocarcinoma/surgery; Lymph Node Excision; Lymphatic Metastasis; Prognosis

RESUMO

A metastização ganglionar constitui um dos fatores prognósticos mais adversos no colangiocarcinoma intra-hepático (CCAi), sendo que a sobrevivência global aos cinco anos raramente excede os 15% nos doentes com doença nodal. O papel e a extensão da linfadenectomia extra-hepática neste contexto permanecem, no entanto, controversos. Esta revisão narrativa sintetiza a evidência atual relativa à avaliação ganglionar no CCAi, incluindo as implicações prognósticas da doença nodal, a previsão pré-operatória de metastização ganglionar, o potencial benefício em termos de sobrevivência da linfadenectomia e a morbilidade pós-operatória associada. O prognóstico é particularmente desfavorável em doentes com múltiplos gânglios metastizados, com um rácio ganglionar elevado ou com metastização para além do ligamento hepatoduodenal. A imagiologia pré-operatória com tomografia computorizada (TC) ou ressonância magnética (RM) apresenta uma acuidade limitada para o estadiamento nodal, enquanto a PET-CT e a ecoendoscopia com punção aspirativa por agulha fina oferecem maior capacidade de deteção em casos selecionados. Para ultrapassar esta limitação, têm sido propostos normogramas preditivos, que integram variáveis clínicas, bioquímicas e radiológicas, estando disponíveis online sob a forma de calculadoras para utilização diária na prática clínica. Do ponto de vista cirúrgico, uma linfadenectomia adequada, definida pela colheita de pelo menos seis gânglios, mantém-se essencial para um estadiamento rigoroso e deve ser adaptada em função da localização do tumor, envolvendo as estações 1, 3, 7, 8 e 12 nos tumores do lobo esquerdo e as estações 8, 12 e 13 nos tumores do lobo direito. Embora o seu papel terapêutico continue a ser debatido, um número crescente de estudos publicados nos últimos anos sugere que a linfadenectomia poderá conferir um benefício em termos de sobrevivência, particularmente em doentes cN0 submetidos à resseção R0 e em casos com biologia tumoral menos agressiva.

Palavras-chave: Colangiocarcinoma/cirurgia; Linfadenectomia; Metastização Ganglionar; Prognóstico

INTRODUCTION

Cholangiocarcinoma (CCA) is the second most common primary liver malignancy after hepatocellular carcinoma and represents a highly aggressive group of biliary tract cancers. In clinical practice, cholangiocarcinomas are classified by their anatomical location within the biliary tree. The majority—about 80%–90% —are extrahepatic: among these, approximately 50%–60% are perihilar (or hilar) tumors, while 20%–30% are distal cholangiocarcinomas. The remaining 10%–20% are intrahepatic cholangiocarcinomas (iCCA), arising within the hepatic parenchyma from the biliary ducts beyond the second-order branches of the biliary tree.[1]

Several risk factors have been associated with cholangiocarcinoma, including obesity, metabolic syndrome, tobacco smoking, and chronic liver disease (e.g. viral hepatitis, cirrhosis).[2–4]

In extrahepatic cholangiocarcinomas, the role of extrahepatic lymphadenectomy is relatively well established and incorporated in many guidelines and surgical protocols[5–7]; thus, extrahepatic CCA is not the primary focus of this review. In contrast, for iCCA, although associations such as AJCC (American Joint Committee on Cancer), ESMO (European Society for Medical Oncology), NCCN (National Comprehensive Cancer Network), and AHPBA (American Hepato-Pancreato-Biliary Association) recommend lymph node assessment, the extent, indications, and impact of extrahepatic lymphadenectomy in iCCA remain controversial.

Indeed, in the literature, there is a wealth of retrospective studies addressing lymph node involvement in iCCA, but no prospective phase III randomized trial to definitively clarify the benefit. Many recent publications—even in 2025—conclude along similar lines: "data are scarce and prevent from solid conclusions."

Why, then, should this controversy continue to be debated? The answer lies in the poor prognosis of iCCA and the potential impact that accurate nodal staging or therapeutic lymphadenectomy might have in improving outcomes. The prognosis for iCCA remains dismal: only about 15% of patients

are considered candidates for surgical resection.[8] Among those, 50%–70% will experience recurrence (particularly at distant sites). The 5-year overall survival (OS) rate after diagnosis is generally reported in the range of 25%–40%.[9,10]

Even in early-stage lesions (e.g. T1 tumors), there is a non-negligible risk (≈15%–20%) of lymph node metastasis (LNM), underscoring the biological aggressiveness of nodal dissemination in iCCA.[11] LNM is a strong adverse prognostic factor: for example, 3-year OS may reach ~56% in pN0 patients but drops dramatically to 0%–15% in pN+ patients (depending on series).[12,13] Given the poor prognosis, every available tool should be considered in an attempt to improve survival, while adhering to the principle of non-maleficence. Therefore, the risk–benefit balance of an extended lymphadenectomy must be carefully evaluated.

This review aims to critically appraise and synthesize the current evidence regarding the prognostic significance of lymph node status in iCCA, to evaluate the accuracy and limitations of preoperative nodal assessment, to examine the rationale and optimal extent of lymphadenectomy, and to discuss its potential therapeutic role within the surgical management of iCCA.

DEFINITION OF EXTRAHEPATIC LYMPHADENECTOMY

The liver generates an exceptionally high volume of lymph—estimated at 1 to 3 L per day, which accounts for nearly half of the thoracic duct flow in adults. The majority of this lymph (>80%) drains through the periportal lymphatic system, which runs alongside the portal triads in the same direction as bile. Consequently, the first nodal basins are typically the hilar lymph nodes and peripancreatic nodes.[14]

However, hepatic lymphatic drainage is far from linear. The liver contains both deep and superficial lymphatic systems, which together create multiple and sometimes unpredictable outflow pathways.[15,16]

- Deep lymphatic system: This includes the periportal network and the hepatic venous system. While most lymph (80%) follows the periportal route to the hilum, some vessels track along the suprahepatic veins and inferior vena cava, draining directly into the posterior mediastinum. Others pass through the hepatorenal ligament and reach the paraaortic lymph nodes and cisterna chyli (Fig. 1).
- Superficial lymphatic system: Located within the subserosal connective tissue, this system can be divided into two compartments (Fig. 2):

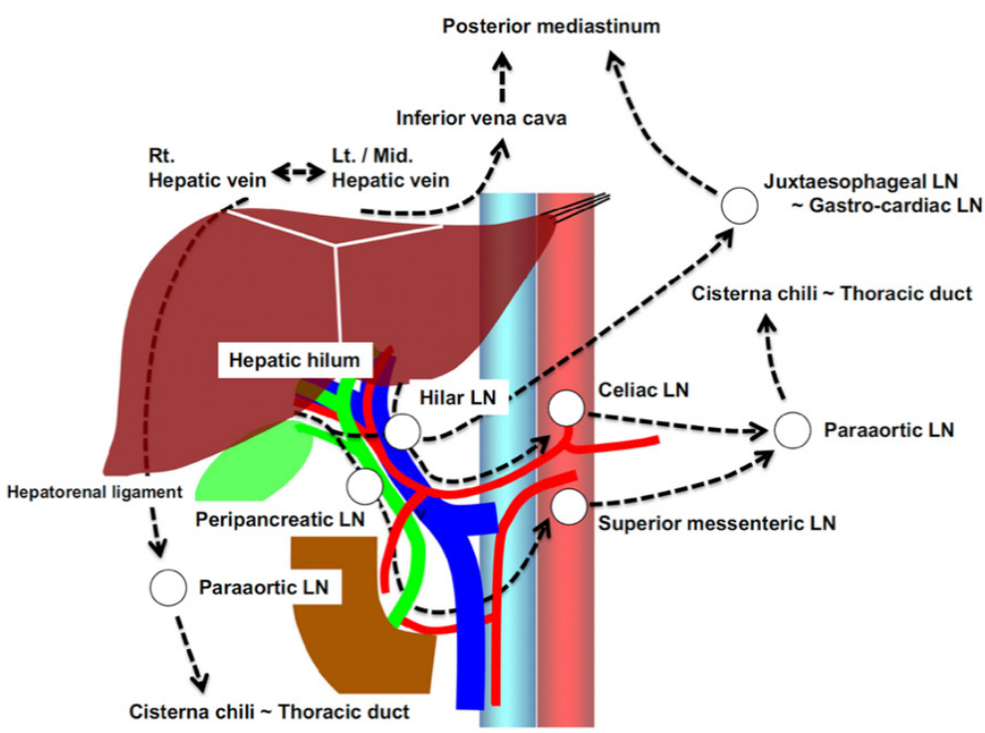

Figure 1 – Schematic representation of the deep hepatic lymphatic drainage.

Adapted from: Morine Y, Shimada M. J Gastroenterol. 2015; 50:913-27.[15]

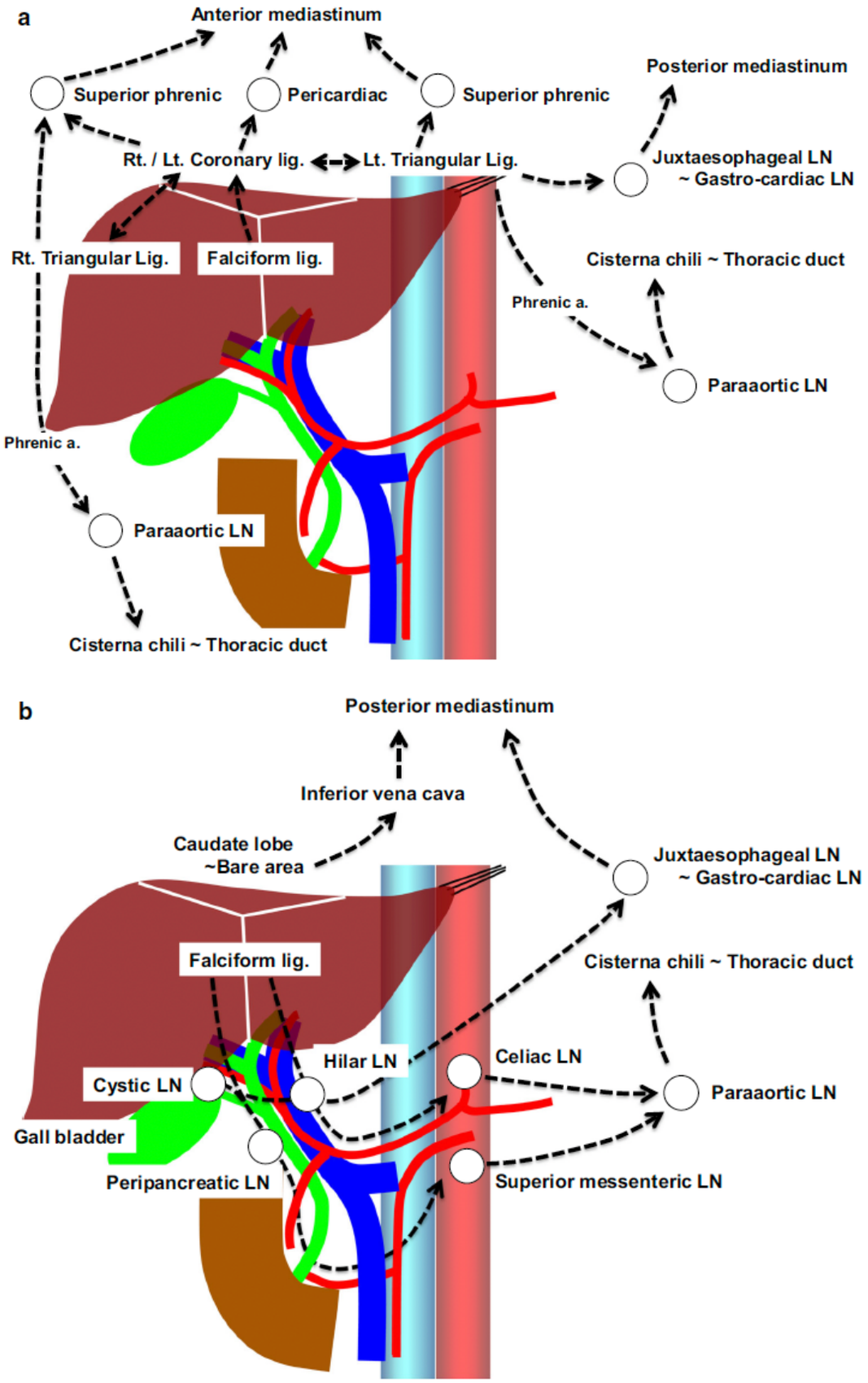

Figure 2 – Schematic representation of the superficial hepatic lymphatic drainage; **a** – convex surface of the liver; **b** – inferior surface of the liver.

Adapted from: Morine Y, Shimada M. J Gastroenterol. 2015; 50:913-27.[15]

- From the convex hepatic surface, lymphatic vessels course along the coronary, triangular, and falciform ligaments, draining into pericardial, superior phrenic, and juxtaesophageal lymph nodes. From there, they communicate with the anterior mediastinum and paraaortic nodes.
- From the inferior hepatic surface, lymphatic vessels converge toward the hilum and regional hilar nodes. Additional vessels from the caudate lobe and bare area accompany the inferior vena cava and connect directly to posterior mediastinal nodes.

Because of these multidirectional routes, skip metastases—distant nodal involvement in the absence of hilar node disease—are not uncommon in iCCA. Moreover, the definition of "regional lymph nodes" varies according to tumor location within the liver.[17]

According to the 8th edition AJCC staging system[18]:

- For right-lobe iCCA, extrahepatic lymphadenectomy should include stations 12 (hepatoduodenal ligament), 8 (common hepatic artery), and 13 (retropancreatic and periduodenal nodes) – Fig. 3a.
- For left-lobe iCCA, in addition to stations 12 and 8, dissection should include stations 1 (right paracardial), 3 (lesser curvature), and 7 (left gastric artery nodes) – Fig. 3b.

Despite these proposed anatomical templates, the definition and extent of lymphadenectomy in iCCA remain poorly standardized. Most published studies fail to specify which nodal stations were dissected, and very few report whether the AJCC-recommended minimum of six lymph nodes for staging was achieved.[19,20] This lack of standardization, coupled with the multidirectional nature of hepatic lymphatic drainage contributes to the ongoing controversy about the prognostic and therapeutic value of extrahepatic lymphadenectomy in iCCA.

Although the AJCC/UICC TNM system defines adequate nodal staging in iCCA as the retrieval of ≥6 lymph nodes and classifies nodal status as N0 (no metastatic nodes) or N1 (one or more metastatic nodes), real-world practice lags behind these standards. Large multicenter and registry analyses show that only about half of patients undergoing resection for iCCA have pathologic assessment of even one regional lymph node, reflecting inconsistent performance of lymphadenectomy and under-staging in routine care.[21–24]

PROGNOSTIC IMPACT OF LYMPH NODE METASTASES

In the current 8th edition of the AJCC Cancer Staging Manual, lymph node spread confined to the regional basin—classified as N1 disease—is no longer considered stage IVa, but has been reclassified as stage IIIB. In contrast, involvement of celiac, peri-aortic, or caval lymph nodes is regarded as distant metastasis (M1) and therefore staged as stage IV.[18]

The presence of regional LNM carries a profound adverse prognostic impact. Across large retrospective and

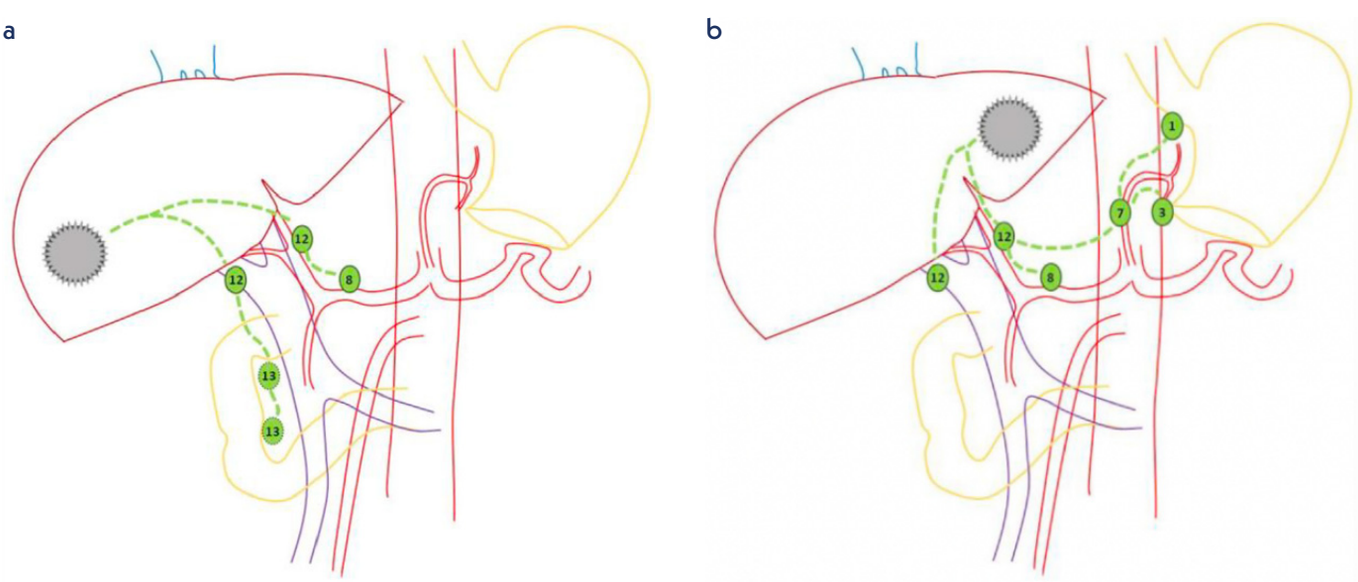

Figure 3 – Schematic representation of lymph nodal stations for: **a** – right-located iCCA; **b** – left-located iCCA.

Adapted from: Sposito C, et al. Eur J Surg Oncol. 2022;48:150–9.[17]

population-based cohorts, nodal involvement is consistently associated with a 2- to 3-fold increased risk of death compared with node-negative disease.[25,26] Following liver resection, patients with LNM experience a median survival of only 15–20 months, and their 5-year OS does not exceed 15%. These figures have been reproduced in multiple registry-based and institutional series, underscoring lymph node status as one of the most powerful prognostic factors in iCCA.[22,25,27]

1. NUMBER OF METASTATIC LYMPH NODES

With the growing understanding of the role of lymphadenectomy in cholangiocarcinoma, it has become evident that not only nodal status (pN0 vs pN+), but also the number of metastatic lymph nodes is strongly associated with patient survival.

One of the first studies to highlight this relationship was published in 2015 by the Johns Hopkins Hospital group in Baltimore. In this series, 749 patients who underwent curative-intent resection for iCCA were analyzed, of whom 64% were pN0 and 36% pN+. The authors demonstrated that the presence of ≥2 metastatic lymph nodes was significantly associated with worse OS. Specifically, they reported a 26% increased risk of death for each additional metastatic node, underlining the substantial prognostic impact of nodal burden.[28]

Subsequently, a multicenter study led by Zhang *et al* confirmed these findings. In this analysis, the number of metastatic lymph nodes emerged as an independent predictor of OS. Median survival was markedly stratified according to nodal burden: 45 months in patients without nodal metastasis, 19.8 months in those with 1–2 positive nodes, and only 16 months when ≥3 nodes were involved. These results further emphasize the prognostic significance of the absolute number of metastatic lymph nodes in iCCA.[22]

Given these observations, subsequent studies have sought to refine prognostic assessment by considering not only the absolute number of positive nodes, but also the lymph node ratio.

2. LYMPH NODE RATIO

The lymph node ratio (LNR), defined as the number of metastatic lymph nodes divided by the total number of examined lymph nodes, has emerged as an important prognostic indicator in several malignancies. One of the earliest studies to investigate its prognostic value in iCCA was conducted at the Mayo Clinic and published in 2015.[25] In this retrospective analysis of 164 patients who underwent hepatic resection with lymphadenectomy, the authors demonstrated that LNR was independently associated with OS.

Specifically, patients with an LNR greater than 0.1 exhibited significantly worse survival outcomes compared with those with lower ratios. The study reported that LNR outperformed the simple dichotomous classification of lymph node status (positive versus negative) in predicting long-term outcomes. Importantly, the adverse prognostic impact of LNR > 0.1 persisted even after adjusting for other clinicopathological variables in multivariate analysis.

Subsequently, a larger multicenter analysis further investigated the prognostic implications of LNR in iCCA.[29] This study evaluated a total of 1425 patients, of whom 212 underwent surgical resection while the remaining received chemotherapy alone. Among patients who achieved an R0 resection, surgical treatment conferred a survival advantage regardless of the LNR. By contrast, in the subgroup of patients who underwent an R1 resection, a survival benefit was observed only when the LNR was ≤ 0.5, whereas patients with higher ratios did not derive a significant advantage from surgery.

These findings underscore two important aspects: first, the pivotal role of achieving an R0 resection in iCAA, which appears to outweigh the negative prognostic impact of LNM; and second, the nuanced influence of LNR in the context of incomplete resections, where its prognostic significance becomes more apparent.

In a more recent large retrospective analysis,[30] the prognostic significance of LNR was evaluated in patients undergoing primary surgical resection with lymphadenectomy (≥4 nodes harvested) for both intra-hepatic and extra-hepatic cholangiocarcinoma.

The cohort comprised 954 patients with iCCA and 1607 with extra-hepatic cholangiocarcinoma. For the ICC subgroup, median OS was 62.7 months in patients with LNR = 0 (i.e., no positive nodes), 40.8 months in those with LNR < 0.3, and 25.2 months when LNR ≥ 0.3 ($p < 0.001$).

On multivariate Cox regression adjusting for age, sex, comorbidity score (Charlson–Deyo), histology, margin status, chemotherapy and radiotherapy, both LNR <0.3 (HR 2.1; 95% CI 1.6–2.7) and LNR ≥0.3 (HR 2.94; 95% CI 2.3–3.8), when compared with LNR = 0, were independently associated with worse OS in ICC. Furthermore, when LNR <0.3 was taken as the reference, LNR ≥0.3 remained significantly associated with inferior OS (HR 1.53; 95% CI 1.2–2.0).

3. ROLE OF LYMPH NODE STATION

Although there is no absolute consensus among published series, accumulating evidence suggests that the specific lymph node station involved carries prognostic significance in cholangiocarcinoma. A Japanese study published in 2011 provided one of the earliest insights into this issue.[31] The authors evaluated 93 patients with cholangiocarcinoma, including 61 who underwent surgical resection and 32 deemed unresectable. Strikingly, patients with metastasis to the gastrohepatic lymph nodes demonstrated survival outcomes comparable to those in the unresectable cohort, with no survivors observed in this subgroup at two years of follow-up. Moreover, the study highlighted that metastasis to the gastrohepatic or para-aortic stations was invariably associated with concomitant involvement of the hepatoduodenal ligament (station 12) or the common hepatic artery (station 8).

A more recent landmark study by Zhang *et al*, published in 2021, further clarified the prognostic importance of lymph node station in iCCA.[22] This large-scale international collaboration involved 15 high-volume centers worldwide and included 603 patients who underwent surgical resection with lymphadenectomy. The analysis demonstrated that the anatomical location of nodal metastasis had a significant impact on survival outcomes. Specifically, patients with LNM confined to station 12 achieved a median OS of 20 months, whereas the presence of nodal metastases beyond station 12 was associated with worse outcomes, with a median survival of only 15 months.

These findings highlight that the prognostic impact of nodal disease in iCCA depends not only on the presence of metastases but also on their anatomical distribution. Furthermore, the study supports the concept that an adequate lymphadenectomy should extend beyond station 12 to ensure accurate staging and optimal prognostic stratification.

4. DECISION ON ADJUVANT TREATMENT

The role of adjuvant systemic therapy following curative-intent resection in biliary tract cancers — including cholangiocarcinoma — has been clarified in part by the landmark BILCAP trial.[32] This was a randomized, controlled, multi-center phase III study comparing six months of oral capecitabine with observation alone in patients who had undergone macroscopically complete resection of biliary tract cancer.

In the intention-to-treat analysis, the median OS was 51.1 months with capecitabine versus 36.4 months with observation (adjusted HR 0.81; 95 % CI 0.63-1.04; p = 0.097). In a sensitivity analysis adjusting for nodal status, tumor grade, and gender, the HR was 0.71 (95 % CI 0.55-0.92; p = 0.010).

In the per-protocol population, median OS was 53.0 months versus 36.0 months (adjusted HR 0.75; 95 % CI 0.58-0.97; p = 0.028). These results have been interpreted as supporting the adoption of adjuvant capecitabine as the standard of care in the post-resection setting for biliary tract cancers.

Importantly, subgroup analyses and retrospective meta-analyses have suggested that the most pronounced benefit is observed among patients at higher risk — namely those with node-positive status (pN +) and/or R1 margin resection. Although the BILCAP trial was not powered to definitively prove benefit specifically in those subgroups, the data provide a strong rationale to consider adjuvant capecitabine, particularly in patients with nodal metastases or close/positive margins.

From the perspective of lymphadenectomy and lymph node assessment in cholangiocarcinoma, an adequate nodal dissection is critical for optimal decision-making. Performing a proper lymphadenectomy enables accurate determination of nodal status (pN0 vs pN +) and potentially even LNR or station involvement. This in turn, better informs risk stratification and selection for adjuvant therapy. Without an adequate nodal assessment, some patients with occult nodal disease may be misclassified as low-risk and thereby may miss the opportunity to benefit from adjuvant treatment. Conversely, knowing that a patient has nodal involvement supports the decision to offer adjuvant capecitabine, given the higher risk of recurrence and poorer prognosis.

In fact, preliminary work from Pawlik and colleagues highlighted the critical importance of lymph node staging for long-term prognostic stratification in iCCA.[21] In their analysis, nodal assessment was identified as an essential determinant of survival outcomes, surpassing other clinicopathological variables in prognostic significance. Importantly, the study demonstrated that in the absence of lymph node information, it becomes exceedingly difficult to counsel patients accurately regarding prognosis.

The authors showed that tumor-related factors traditionally considered relevant for prognostication — such as T category — including vascular invasion, and the distinction between unifocal and multifocal disease — retained predictive value only in pN0 patients. Conversely, in pN1 patients, prognosis

was overwhelmingly dictated by the presence of metastatic disease within the lymphatic basin, rendering T-related features largely irrelevant.

This study therefore reinforced the concept that nodal status is not only a staging parameter but also a decisive prognostic determinant, and that omission of adequate lymphadenectomy compromises both prognostic accuracy and the capacity to guide postoperative therapeutic decisions.

PREDICTORS OF LYMPH NODE METASTASES

Given the pivotal role of nodal status in determining prognosis and guiding therapeutic strategies, accurate preoperative identification of LNM is of paramount importance to appropriately balance the risks and benefits of lymphadenectomy. However, the available literature on preoperative assessment of nodal disease in iCCA remains limited. Current radiological modalities, including computed tomography (CT) and magnetic resonance imaging (MRI), have demonstrated suboptimal sensitivity and specificity, often underestimating the true extent of nodal involvement. As a result, significant interest has emerged in defining clinicopathological predictors of LNM that may assist in risk stratification and guide the surgical and perioperative decision-making process.

1. COMPUTED TOMOGRAPHY

Across the available literature, there is consistent agreement that the diagnostic performance of CT for predicting LNM in iCCA is limited.[24,33–36] The positive predictive value (PPV) of CT is notably low, undermining its role as a reliable preoperative staging tool. A lymph node short-axis diameter greater than 10 mm has traditionally been used as the main radiological criterion for suspicion of nodal metastasis; however, this threshold is associated with a PPV of only approximately 28%. This poor performance is largely explained by the frequent occurrence of reactive nodal hyperplasia secondary to cholestasis, inflammation, or biliary obstruction, which can result in nodal enlargement in the absence of metastatic disease.

Other morphological features, such as ring-like enhancement and contrast uptake, have been shown to increase the specificity of CT in identifying true nodal metastases. Nevertheless, these imaging characteristics are relatively uncommon, and only a minority of patients present with such findings in the preoperative setting. As a result, despite incremental refinements, CT remains an imperfect modality for nodal staging, with a high risk of underestimating or misclassifying lymph node involvement.

2. MAGNETIC RESONANCE IMAGING

Among the available evidence on MRI for preoperative lymph node staging in cholangiocarcinoma, particular attention has been given to the Cholangiocarcinoma Screening and Care Program (CASCAP) in Thailand.[37] This nationwide initiative was developed in a region endemic for *Opisthorchis viverrini* infection, a well-established risk factor for biliary tract malignancy. Given the high incidence of cholangiocarcinoma in this population, MRI was implemented as a screening and diagnostic tool to improve early detection and staging accuracy.

However, the results were far from encouraging. In the CASCAP study, MRI accurately identified the presence or absence of LNM in only 29 of 51 cases of cholangiocarcinoma. Overall, MRI achieved a sensitivity of 57.1%, a specificity of 56.7%, a VPP of 48.0%, and a negative predictive value (NPV) of 65.4%. These findings highlight the limited reliability of MRI in assessing nodal disease, despite its theoretical advantages in soft-tissue contrast and multiplanar capability.

Thus, although MRI represents an indispensable modality for local tumor assessment and liver mapping in cholangiocarcinoma, its role in lymph node staging remains suboptimal, and its performance is not sufficiently robust to guide clinical decision-making on lymphadenectomy or adjuvant treatment planning.

3. POSITRON EMISSION TOMOGRAPHY (PET-CT)

Multiple studies examining the utility of PET-CT in patients with iCCA suggest that this modality offers better predictive performance for LNM than conventional imaging. For example, one institutional series reported that PET-CT achieved a sensitivity of 84%, specificity of 86% and an overall accuracy of 86% for the detection of regional nodal metastases in 90 patients with histologically confirmed iCCA.[38]

Another meta-analysis found that PET-CT had an area under the ROC curve (AUC) of ≈ 0.77 for N-staging, with specificity notably higher than MRI (0.92 *vs* 0.69).[39]

Importantly, PET-CT appears to perform best when applied to lymph nodes of larger size (e.g., short-axis diameter > 10 mm) in which metabolic uptake differences are more readily distinguished. Smaller nodal metastases often escape detection due to the limited spatial resolution and partial-volume effects of PET imaging. In the context of iCCA,

PET-CT has also been shown to uncover occult metastatic disease (regional or distant) in approximately 20%-30% of patients initially believed to have localized disease on CT/MRI — underscoring its importance in comprehensive staging and surgical planning.[40,41]

4. ENDOSCOPIC ULTRASOUND WITH FINE-NEEDLE ASPIRATION (EUS-FNA)

EUS-FNA has gained increasing use in the preoperative setting to identify clinically positive lymph nodes (cN+). Despite its expanding application, data specifically addressing iCCA remains limited. One of the most relevant contributions comes from a retrospective study conducted at the Mayo Clinic.[42]

In this series, 157 patients with cholangiocarcinoma were evaluated, of whom 133 underwent EUS-FNA for nodal assessment. The diagnostic yield of EUS-FNA for LNM was markedly superior to that of CT: 86% *vs* 47%, respectively. Importantly, preoperative detection of nodal metastases was achieved in 27 of the 31 patients who were ultimately confirmed as pN+ on final pathology.

Nevertheless, while these findings are encouraging, the generalizability of EUS-FNA to iCCA is not yet fully established, and prospective validation is required. In particular, its role relative to other modalities such as PET-CT and MRI, and its integration into routine preoperative staging algorithms, remains to be clearly defined.

5. NOMOGRAMS FOR PREDICTING LNM

Given the limited accuracy of conventional imaging modalities in detecting clinically positive lymph nodes in iCCA, several groups have attempted to develop predictive nomograms that integrate clinical, biochemical, and radiological variables. These tools aim to overcome the diagnostic gap of CT and MRI, thereby improving preoperative staging.

One of the first and most influential efforts in this field was published by Pawlik's group.[43] In their multicenter analysis, the authors developed and validated a nomogram specifically designed to predict the likelihood of LNM in iCCA. The model demonstrated high accuracy and robust discriminative ability. Variables incorporated into the nomogram included patient age, number of hepatic lesions, serum CA 19-9 level, albumin, and total bilirubin.

Importantly, this predictive tool has been made available as an online calculator, thereby facilitating its incorporation into routine clinical practice.

In addition to the work by the Pawlik group, a more recent predictive model was developed and published by Sposito's group.[44] This nomogram was derived from a large multicenter Italian cohort including seven high-volume centers, where 693 patients with iCCA underwent curative-intent surgery with adequate lymphadenectomy (≥6 lymph nodes).

In this study, several variables were identified as independent risk factors for nodal metastasis: preoperative CA 19-9 level, radiologically suspicious lymph nodes, patient age, and the tumor burden score — a composite metric integrating tumor size and focality (uni- versus multifocal disease). These variables were incorporated into a predictive model that demonstrated excellent accuracy in estimating the probability of nodal involvement. Importantly, a progressive increase in the incidence of pN+ disease was observed across risk groups defined by the model: from 30% in the low-risk group to 87% in the high-risk group. Similar to the nomogram proposed by the Pawlik group, the Sposito model has also been made available online.

By allowing individualized risk assessment of nodal metastasis, the nomogram provides clinicians with a pragmatic instrument to guide decisions on surgical planning and lymphadenectomy strategy.

SURVIVAL BENEFIT OF LYMPHADENECTOMY

Among all aspects of lymphadenectomy in iCCA, perhaps none has generated more controversy than the question of whether lymphadenectomy translates into a survival benefit. Indeed, if a clear survival advantage was firmly established for patients undergoing lymphadenectomy compared with those who did not, this would likely not remain one of the most debated "hot topics" in surgical oncology.

A comprehensive meta-analysis published by Zhou and colleagues in 2019 directly addressed this issue.[45] The authors pooled data from 13 studies, including a total of 1377 patients with iCCA who underwent hepatic resection, with or without lymphadenectomy. The analysis demonstrated no significant difference in OS between the two groups. However, the authors acknowledged that the available evidence was limited by several methodological constraints: many of the included studies were retrospective in nature, derived from single institutions, and involved relatively small patient cohorts.

Another important study that must be cited in this context is the work published by Sposito and colleagues from the

National Cancer Institute of Milan.[46] In this large retrospective analysis, the authors evaluated 706 cN0 patients with iCCA who underwent curative-intent resection. Among them, 417 patients (59%) had an adequate lymphadenectomy, defined as retrieval of ≥6 lymph nodes.

The study provided important insights into the prognostic role of lymphadenectomy. In the subgroup of patients with pathological nodal involvement (pN+), those who underwent an adequate lymphadenectomy experienced significantly improved OS and recurrence-free survival compared with those with inadequate nodal dissection ($p < 0.01$). Notably, this survival benefit was most pronounced in patients with less advanced disease, specifically those with single tumors, tumor size < 5 cm, and serum CA 19-9 < 200 U/mL.

These findings suggest that while lymphadenectomy may not universally improve outcomes across all patients with iCCA, it appears to confer a survival advantage in selected subgroups, particularly those with limited tumor burden and biologically less aggressive disease.

More recently, in the current year (2025), two discordant studies have been published, further fueling the ongoing debate. The first, reported by Zhang and colleagues in March 2025,[47] was a retrospective single-center study from an oncological hospital in China including 308 patients who underwent resection for iCCA. When comparing patients who underwent lymphadenectomy with those who did not, no benefit in OS or disease-free survival was observed. Conversely, the lymphadenectomy group demonstrated higher perioperative morbidity, with longer operative times, increased risk of intraoperative bleeding, greater need for red blood cell transfusion, and prolonged hospital stay. These findings reinforce the concern that routine lymphadenectomy may increase surgical risk without providing oncological benefit in unselected patients.

By contrast, in July 2025, Yu and colleagues published a meta-analysis including 21 retrospective studies.[48] Their pooled analysis revealed that, among cN0 patients, lymphadenectomy was associated with significantly improved OS ($p < 0.01$). Similarly, in the subgroup of patients who underwent R0 resection, lymphadenectomy conferred a survival benefit ($p < 0.01$). However, in patients who had an R1 or R2 resection, lymphadenectomy was paradoxically associated with worse OS ($p < 0.01$).

Another theoretical advantage of systematic lymphadenectomy in iCCA would be its potential role in preventing locoregional recurrence, particularly obstructive jaundice caused by nodal relapse. In principle, a prophylactic lymphadenectomy could decrease the likelihood of regional disease progression leading to biliary obstruction and jaundice. However, no evidence to date has demonstrated this benefit. This is most likely explained by the biological pattern of recurrence in iCCA, which predominantly manifests as distant rather than regional disease.[49–51]

In conclusion, the survival benefit of lymphadenectomy remains a matter of controversy and is far from fully clarified. A central unresolved question is whether nodal disease in this setting should be considered a potentially curable locoregional event or, conversely, an indicator of systemic disease biology. Current evidence suggests a tendency to tip the scale toward a benefit of lymphadenectomy in carefully selected patients, particularly those who are clinically node-negative (cN0) and undergo an R0 resection, especially when the tumor exhibits less aggressive features. These observations highlight the importance of adequate surgical staging and patient selection, while underscoring the persistent need for prospective studies to definitively establish the therapeutic value of lymphadenectomy in iCCA.

POST-OPERATIVE COMPLICATIONS

Lymphadenectomy in the setting of iCCA is not a procedure free of risks. These patients are exposed to an increased likelihood of biliary tract devascularization (including the common bile duct), delayed gastric emptying (notably in left-lobe resections), vascular injury and chylous ascites. According to the literature review, lymphadenectomy is indeed associated with a higher rate of postoperative complications—though one must interpret the data cautiously given the potential confounding by the fact that lymphadenectomy is often performed in more advanced tumors.[48,52,53] In cirrhotic patients, for example, lymphadenectomy was associated with a postoperative complication rate of 71% compared with 23% in non-cirrhotic patients.[54]

Patients with impaired liver function, portal hypertension or underlying chronic liver disease appear particularly vulnerable. Thus, while lymphadenectomy may offer staging or therapeutic advantages, its implementation must be balanced against the increased risk of surgical morbidity in selected patients.

CONCLUSION

At present, surgery remains the only potentially curative treatment for iCCA. LNM represents one of the most adverse

prognostic factors, with median survival after resection reported at 15–20 months and 5-year OS around 15%. Prognosis is particularly poor in patients with a high number of metastatic nodes, elevated lymph node ratio, or metastases beyond the hepatoduodenal ligament. Preoperative staging with CT and MRI has shown limited accuracy, which has prompted the development of predictive nomograms and online calculators to refine risk stratification; however, definitive nodal staging still relies on adequate surgical lymphadenectomy. Given the heterogeneous lymphatic drainage of the liver, nodal dissection should be tailored to tumor laterality, encompassing stations 1, 3, 7, 8 and 12 for left-lobe tumors, and stations 8, 12 and 13 for right-lobe tumors, with retrieval of at least six nodes recommended for accurate staging.

From an oncological perspective, the fundamental controversy remains whether nodal disease in iCCA should be regarded as a potentially curable locoregional event or a marker of systemic spread. While no high-level evidence has definitively demonstrated a survival benefit of lymphadenectomy, selected patients — particularly cN0 individuals undergoing R0 resection — may derive some advantage, and long-term survivors with nodal disease have been reported following aggressive surgery. On the other hand, lymphadenectomy is associated with increased morbidity, especially in cirrhotic patients, and has not been proven to prevent local recurrence. Therefore, its application must always balance potential harms against the benefits of more accurate staging and possible survival impact, pending clarification from well-designed prospective studies.

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