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Review

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The impact of lymphadenectomy on intrahepatic cholangiocarcinoma management and prognosis: a comprehensive review

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Abstract

Intrahepatic cholangiocarcinoma (iCCA) is a rare liver cancer generally associated with poor patient outcomes. Curative intent liver resection has been established as a standard treatment of care of resectable disease. However, the role of lymphadenectomy, including the extent of resection and therapeutic value, continues to be an area of controversy. The objective of this review was to highlight the role of lymph node dissection (LND) relative to therapeutic value and prognosis in the surgical management of iCCA. A comprehensive review was performed using MEDLINE/PubMed. Search terms included “intrahepatic cholangiocarcinoma”, “bile duct cancer”, "lymphadenectomy", “lymph node metastasis”, and "lymph node staging". Treatment for iCCA should include an R0 resection with regional lymphadenectomy. The prognostic and therapeutic value of regional lymphadenectomy has been an increased area of research and debate. An increased number of lymph node metastases has correlated with inferior overall survival versus lymph node-negative disease. In addition to surgical resection, regional lymphadenectomy with the removal of at least six lymph nodes in the appropriate nodal basins based on primary tumor location should be standard. The identification of lymph node metastasis provides additional important information to guide providers in determining adjuvant therapy and surveillance strategies.

Keywords: Intrahepatic cholangiocarcinoma, lymph node dissection, neoadjuvant therapy, precision medicine

INTRODUCTION

Intrahepatic cholangiocarcinoma (iCCA) is an aggressive cancer that originates above the second-order bile ducts[1,2]. As the second most common primary biliary malignancy, iCCA represents 10%-15% of all primary liver tumors and continues to increase in incidence worldwide[3,4]. While surgical resection is the best curative-intent treatment option, 5-year survival after surgical resection is only 20%-30%[5-7]. Systemic treatment continues to evolve in the setting of advanced disease through the use of immune checkpoint inhibitors. As demonstrated in the TOPAZ-1 trial, durvalumab, a PD-L1 inhibitor, when added to gemcitabine/cisplatin, significantly improved median overall survival and is now considered the new standard of care. To this point, immune checkpoint inhibitors have demonstrated efficacy in the advanced disease setting and may be used in the adjuvant treatment setting in the future[8,9]. The need for improved systemic therapy is particularly relevant to patients with iCCA as long-term outcomes following resection are often poor and characterized by tumor recurrence in 50%-70% of patients[5,10]. One of the strongest predictors of tumor recurrence is lymph node metastasis (LNM), which can be present in up to 40%-60% of patients[11,12]. The presence of LNM can be difficult to assess on preoperative clinical imaging and can be present even among patients with early-stage, small tumors[11,12]. As such, lymph node dissection (LND) has been endorsed as the standard of care in the operative approach of patients undergoing resection of iCCA[5,13].

While LND has become more widely adopted in the surgical management of iCCA, the beneficial effect and role of LND remain somewhat controversial. For example, the impact of LND on staging and prognosis, as well as the technical aspects of LND (i.e., which nodal basins require evaluation), continue to be debated. We herein review the role of LND as part of the surgical management of iCCA, with a particular emphasis on LND prognostic and therapeutic value, as well as the technical aspects of LND in the treatment of iCCA.

METHODS

A comprehensive review was performed using MEDLINE/PubMed with the search dates of January 1, 1990 to March 21, 2023. Search terms included "intrahepatic cholangiocarcinoma", "bile duct cancer", "lymphadenectomy", "lymph node metastasis", and "lymph node staging" in PubMed. Articles written in English identified using the aforementioned search terms were included. A review of included manuscripts was performed, and the latest, most relevant articles were included.

MAIN BODY

Lymphadenectomy technique

The incidence of LNM in patients with iCCA ranges from 20%-60%. The National Comprehensive Cancer Network (NCCN) guidelines suggest evaluation of six lymph nodes at minimum to stage patients adequately[14-16]. Zhang *et al.* reported data from a large multi-institutional experience that defined the prognostic impact of number and station of LNM after curative-intent resection for iCCA[14]. Among 603 patients with iCCA who underwent surgery, 40% had LNM. Median overall survival was incrementally worse among patients without nodal disease (N0) (69.8 months) *vs.* 1 to 2 LNM (proposed N1) (26.0 months) versus 3 or more LNM (proposed N2) (16.0 months)[14] [Figure 1]. LNM were more likely to be detected, and thus patients more likely to be staged accurately, when six or more lymph nodes were resected, which was consistent with current American Joint Committee on Cancer (AJCC) guidelines[15,16]. Regarding nodal location and station, median OS was worse in patients who had positive lymph nodes outside the hepatoduodenal ligament (HDL) (station 12) (15.0 months) compared with individuals who had LNM confined to the HDL (20.0 months). In turn, the data suggested that standard lymphadenectomy of at least six lymph nodes, with dissection of nodal station 12 and beyond, was needed to ensure adequate staging.

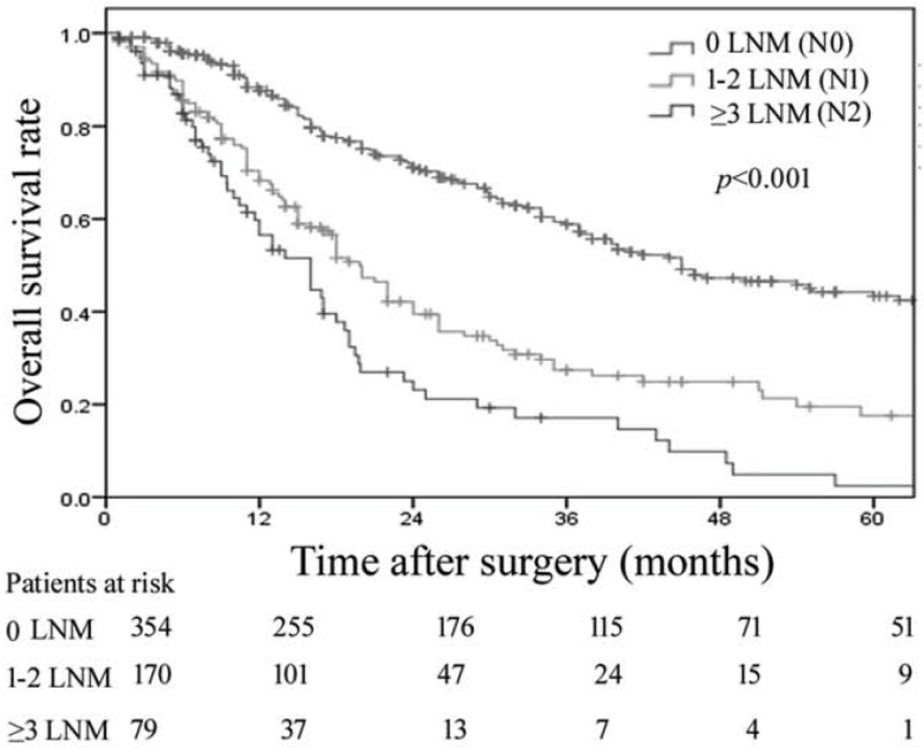

Figure 1. Kaplan-Meier analysis of overall survival (OS) relative to the number of lymph node metastasis. Proposed nodal status was as follows: N0- 0 LNM; N1- 1-2 LNM; N2- 3 or more LNM. Adapted from Zhang *et al.*[14].

The extent of lymphadenectomy for iCCA should be informed by an understanding of the patterns of liver lymphatic drainage related to right versus left-sided iCCA. For example, tumors in the right hemi-liver drain to the HDL (station 12), as well as the peripancreatic (station 13) and hepatic artery (station 8) and celiac (stations 7/9) nodes. In contrast, tumors originating in the left hemi-liver primarily drain to nodes in station 12, as well as to nodes also along the lesser curvature of the stomach (stations 1/3)[17] [Figure 2]. As such, "sidedness" is important to consider when performing LND for iCCA, as the liver is one of the largest lymph-producing organs and lymphatic drainage plays a critical part in cancer dissemination[18]. Importantly, lymph node involvement beyond the primary nodal basins, such as disease within the celiac or para-aortic lymph nodes, represents metastatic disease and curative-intent resection is generally contraindicated as the risk of recurrence/systemic disease can be very high. In one study that evaluated the effect of sidedness on the number and station of LNM, patients who underwent curative-intent surgery for left hemi-liver iCCA had a greater number of lymph nodes resected and had a higher incidence of LNM versus patients with iCCA in the right hemi-liver[5]. However, there was no difference in the station and number of LNM between right- versus left-sided tumors, nor in OS[5]. In aggregate, a minimum of six lymph nodes should be assessed and the extent and location of LND beyond the HDL should be dictated by the location of the iCCA within the liver. By performing an adequate LND relative to number and location, surgeons can better identify the extent of nodal disease and, therefore, better risk stratify patients relative to prognosis, as well as gain information that may assist in decision making regarding adjuvant chemotherapy and surveillance[2,11].

Therapeutic index and lymphadenectomy

Notwithstanding the valuable staging and prognostic information that LND provides, the related therapeutic benefit has been debated. Therapeutic index is a metric that can help define the survival benefit

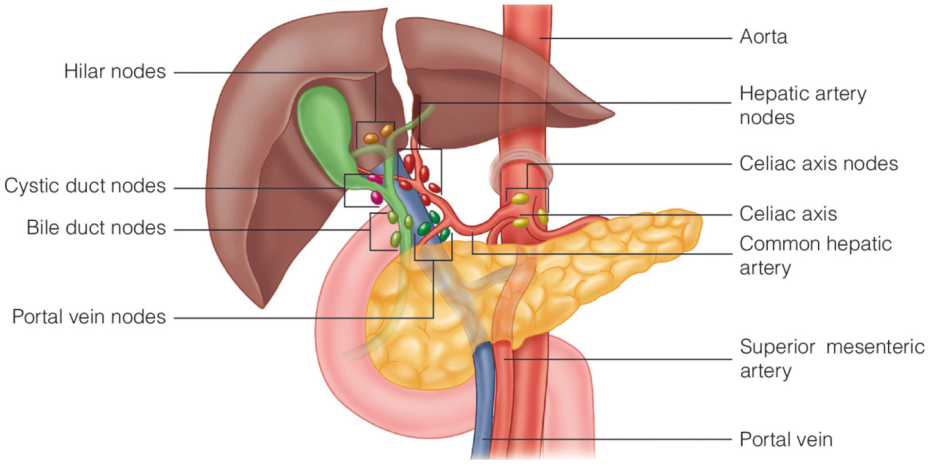

Figure 2. Patterns of lymphatic spread for right and left iCCA. Tumors of the left hemi-liver drain to lymph nodes near the left and common hepatic artery lymph nodes and then toward the celiac axis. Right hemi-liver tumors drain to hepatoduodenal ligament and then peri-pancreatic and aortocaval lymph nodes. Adapted from Compton CC *et al.*[37].

gained from LND and was initially described among patients undergoing surgery for gastric cancer[19,20]. To determine the therapeutic index, LNM frequency in a certain patient group is multiplied by the 3-year cancer-specific survival (CSS) of patients with LNM in that subgroup[20]. Recently, Sahara *et al.* utilized a multicenter institutional database to apply the concept of therapeutic index to iCCA[20]. In this study, roughly one-half (43.5%) of the 471 included patients had positive lymph nodes; the median counts of removed and metastatic lymph nodes were 4 and 0, respectively. The 3-year CSS was 29.9%, with a therapeutic index of 13.0. Of note, patients who had iCCA with major vascular invasion, CEA greater than 5.0, and LNM within nodal basins outside of the HDL had lower therapeutic indices, suggesting these patients may not draw a survival benefit from LND. In turn, while LND may provide prognostic information, LND in patients with high-risk features (i.e., major vascular invasion, high CEA, *etc.*) may not provide a therapeutic benefit given the high likelihood of systemic disease spread. Of note, patients who had seven or more lymph nodes resected had the greatest therapeutic value in patients with positive lymph nodes, suggesting that assessment of more lymph nodes leads to more accurate staging[20]. Interestingly, the presence or absence of LNM may also impact the relative prognostic importance of other modifiable surgical factors such as margin status. For example, Farges *et al.* reported data from the AFC-IHCC-2009 study group and noted no survival differences among patients with margin negative versus margin positive hepatic resection among patients who had LNM[21]. A summary of current consensus guidelines on LND is presented in Figure 3.

PRODIGE 12-ACCORD 18 trial

In addition to helping stratify patients relative to long-term prognosis, data derived from LND may help guide the use of adjuvant therapy. The PRODIGE 12-ACCORD 18 Trial was a multicenter prospective randomized controlled trial that included 196 patients who underwent an R0/R1 resection of a biliary tract cancer[22]. There were 86 (43.9%) patients with iCCA included in the cohort. Patients were randomized to either adjuvant doublet gemcitabine-oxaliplatin (GEMOX), which had been standard of care for advanced biliary tract cancers, or standard surveillance. The primary endpoints were relapse-free survival (RFS) and health-related quality of life (HRQOL). Of note, median RFS (GEMOX 30.4 months *vs.* surveillance 18.5 months, $P = 0.48$), 3-year RFS (47% *vs.* 43%), or OS (75.8 months *vs.* 50.8 months, $P = 0.74$), or HRQOL were not significantly different among groups [Figure 4]. Consequently, adjuvant GEMOX was not recommended for use in biliary tract cancers including iCCA.

Organization	Year	Preoperative evaluation	Diagnostic laparoscopy	Extended resections	Lymphadenectomy	Contraindications
NCCN[6]	2019	H&P, labs, CA 19-9, AFP, CT/MRI, ± biopsy, EGD/ Colo	Should be considered	May be necessary	Should be performed	Extrahepatic and distant LN metastases; multifocal liver disease; ± grossly involved porta LNs
AHPBA[7]	2015	H&P, labs, CA 19-9, CEA, CT/MRI, ± PET, ± EUS, ± biopsy	Recommended for patients with high-risk features	Should be considered	Should be considered	Extrahepatic disease, multiple bilobar or multicentric tumors, distant LN metastases
ILCA[8]	2014	H&P, labs, CEA, CA 19-9, AFP, CT/MRI	Insufficient evidence	Recommended if enables R0	Strongly encouraged	Intrahepatic metastases, vascular invasion, obvious LN metastases, advanced cirrhosis

NCCN National Comprehensive Cancer Network; *AHPBA* Americas Hepatopancreatobiliary Association, *ILCA* International Liver Cancer Association, *H&P* history and physical examination, *EGD/Colo* esophagogastroduodenoscopy/colonoscopy, *CT* computed tomography, *MRI* magnetic resonance imaging, *PET* positron emission tomography, *EUS* endoscopic ultrasound, *LN* lymph node

Figure 3. Summary of published consensus guidelines on the indications for resection of intrahepatic cholangiocarcinoma.

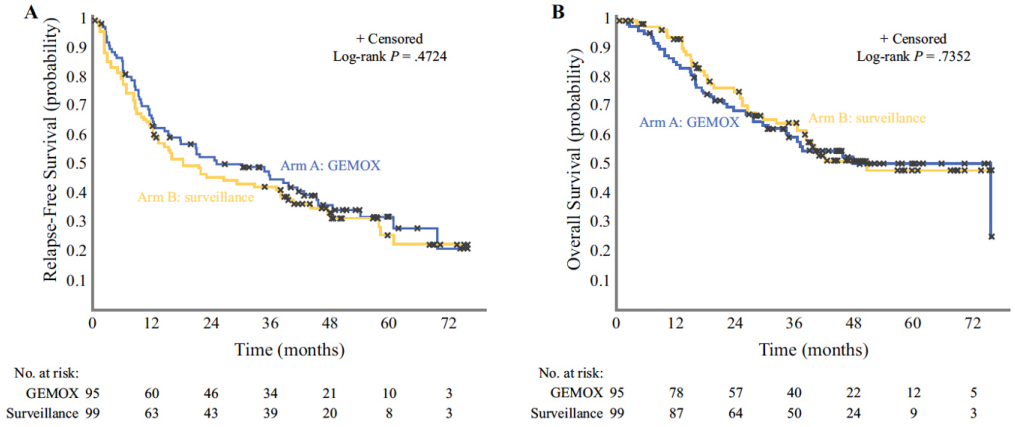

Figure 4. Results from PRODIGE 12-ACCORD 18 trial. (A) Relapse-free and (B) overall survival comparing adjuvant gemcitabine-oxaliplatin versus observation.

The BILCAP trial, a separate prospective adjuvant chemotherapy study, was a multicenter randomized trial completed in the UK from 2006 to 2014. The aim of this study was to compare adjuvant capecitabine, which had been used to treat other gastrointestinal cancers, versus observation[23,24]. In the BILCAP trial, patients were randomized to capecitabine or observation following surgical resection, with the primary outcome being OS. Four hundred forty-seven patients were included in the intention-to-treat arm, with 84 (19%) patients diagnosed with iCCA; 47% of the iCCA patients had LNM. In the per-protocol analysis that adjusted for nodal status, disease grade, and sex, capecitabine was associated with improved OS with a median OS at 53 months versus 36 months in the observation group. As a result of these findings, adjuvant capecitabine is now the standard of care treatment following surgical resection for iCCA[25].

While the PRODIGE trial failed to find a survival benefit for adjuvant GEMOX, the BILCAP study noted an improvement in survival with adjuvant capecitabine following surgical resection. The discrepancies in the data from PRODIGE 12-ACCORD 18 versus BILCAP trials are important to consider relative to LND for iCCA. While the reasons for these differences were undoubtedly multifactorial, one explanation for the discrepancy was that the BILCAP study was enriched with more patients who had adverse pathologic features such as R1 resection margin status and LNM. In turn, adjuvant therapy may simply have a more beneficial effect among patients with poor prognostic factors such as positive margin status and LNM[20,26]. Of note, the ACTICCA-1 trial is a German phase III trial that is currently investigating gemcitabine/ cisplatin versus capecitabine in the adjuvant setting for CCA or gallbladder cancer. The study arms in this

study were chosen based on data obtained from the ABC-02 and BILCAP trials[22,25]. The trial is currently underway and has finished recruitment. Additional adjuvant therapy for biliary tract cancer has also been investigated in the JCOG1202 study. This randomized phase 3 trial was conducted in Japan to examine the efficacy of adjuvant S-1, which was previously studied in other cancers. In this study, patients treated with S-1 had a better 3-year survival (77.1%) compared with patients treated with placebo (67.6%). Although long-term clinical benefits still need to be defined, adjuvant S-1 may be a reasonable adjuvant option for Asian patients following resection of biliary tract cancer[27].

Role of liver transplantation and LND

The use of liver transplantation in the management of iCCA remains controversial. Recently, there has been growing interest in transplant oncology for a variety of cancer indications, including iCCA[28]. A recent meta-analysis conducted by Ziogas *et al.* reported that cirrhotic patients with very early iCCA or select patients with advanced iCCA following neoadjuvant therapy may benefit from transplantation[29]. In a prospective case series, Lundsford *et al.* reported on transplantation of patients with locally advanced unresectable iCCA without extrahepatic disease or vascular involvement who had six months of radiographic disease response or stability following neoadjuvant gemcitabine. Six out of 21 patients eventually underwent transplantation and 1-, 3-, and 5-year OS was 100%, 83.3%, and 83.3%, respectively. Three patients developed recurrent disease after transplantation (median 7.6 months). Given the current scarcity of organs and the indeterminate long-term benefit, transplant for unresectable iCCA should be done on a per-protocol basis for highly selected patients (i.e., no extrahepatic disease, nodal disease, vascular invasion, *etc.*)[28,30-32].

Limitations

Data in the current review need to be interpreted in light of several strengths and limitations. While we provided an overview of the role of LND for iCCA in light of the recently published data, the field of medicine related to iCCA continues to evolve quickly. In particular, a rapidly emerging understanding of the molecular pathogenesis and the varied mutational profile of iCCA has ushered in an era of targeted precision medicine. Multiple studies have recently examined the impact of targeted therapy among patients with and without actionable mutations relative to long-term survival[33,34]. In the future, the relative importance of LND and the presence of LNM may change in the future as these therapies are introduced into the treatment paradigm of patients with iCCA.

CONCLUSIONS

iCCA is an aggressive biliary tract malignancy generally with a poor 5-year survival of 20%-30% even after curative-intent surgical resection. For this reason, additional data regarding staging and prognosis is critical to help risk stratify patients and guide adjuvant chemotherapy. The role of LND in iCCA continues to evolve with more data supporting the use of routine LND with the goal of obtaining at least six lymph nodes and examination of nodes beyond station 12. Important attention to the sidedness of the primary tumor dictates the extent and location of LND. An increased number of lymph node metastases portends more aggressive disease. In general, patients with LNM may benefit the most from adjuvant chemotherapy based on data from the BILCAP trial. In the future, translational studies are needed to clarify the mechanisms involved in lymphatic spread. iCCA has a rich stroma consisting of cancer-associated fibroblasts that promote early metastatic spread. Pre-clinical studies have demonstrated that lymphatic spread may be mitigated through the targeting of fibroblasts and lymphatic endothelial cells via PDGFR pathway inhibition. Therefore, the inhibition of fibroblasts or PDGF-induced signals may represent an effective method to block tumor-associated lymphangiogenesis[35,36].

While additional randomized data are still required to fully understand the role of LND in iCCA, the current data indicate that standard lymphadenectomy of at least six lymph nodes beyond station 12 is strongly recommended. The proposed new nodal staging of N0, N1 and N2 should also be further investigated as a means to better understand outcomes among patients after curative-intent resection of iCCA. Currently, for patients with resectable disease, we recommend surgical resection of the primary tumor with a LND of at least six lymph nodes.

DECLARATIONS

Authors' contributions

Writing of the manuscript, data collection, data interpretation, critical revision and approval of the final manuscript: Gavriilidis P, Bath NM, Pawlik TM

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Conflicts of interest

Not applicable.

Ethical approval and consent to participate

Not applicable.

Consent for publication

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