



## Do Lymph Nodes Matter in Intrahepatic Cholangiocarcinoma?

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A mentor in fellowship training used to emphasize that “surgical oncology is the surgery of lymph nodes.” In our current staging system for cancer, the TNM classification relies on knowing the status of lymph nodes for selection of therapy and prognostic information. In the gastrointestinal tract, positive lymph nodes are used to determine eligibility for both neoadjuvant and adjuvant therapy for tumors in the esophagus, stomach, colon, and rectum. In general, lymph node involvement portends a worse prognosis and the rationale for additional treatment is to mitigate the risk of recurrence following resection and/or downstaging of disease prior to resection. However, in the primary liver tumor space, location and extent of lymphadenectomy has not been widely adopted owing to several factors including lack of prospective data of benefit and until recently, limited role for perioperative therapy. Another challenge has been the American Joint Commission on Cancer (AJCC) guidelines for hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC) that up to the 6th edition were coded together. In the AJCC 7th edition, regional lymph nodes metastases were considered stage IVA disease for ICC. More recently, the AJCC 8th edition made some significant changes including changing the status of positive lymph nodes to stage IIIB disease for ICC and encouraging at least six nodes be examined for proper staging. As these changes occurred over a significant time period over the last 10 years and the recent adoption of adjuvant therapy for biliary tract cancers, it has been difficult to ascertain the impact of these changes and how they should be implemented into current practice.

In the current study, the authors utilized the National Cancer Database (NCDB) to examine the trends of lymphadenectomy in the USA across demographic, geographic, and socioeconomic areas to predict outcomes in this disease.<sup>1</sup> They reported that, in a cohort of 6500 patients with ICC between 2010 and 2019, only 17% of patients received an adequate lymphadenectomy as defined by at least 6 lymph nodes, although this has increased over the time period studied. In addition, 40% of patients did not undergo a lymphadenectomy at all and were considered Nx. This is not particularly surprising since the AJCC 7th edition was released in 2010 and the 8th edition in 2018. However, there was marked variation between regions in adoption of lymphadenectomy, with the Northeast being an outlier in noncompliance. The patients most likely to undergo lymphadenectomy for ICC were found to be younger, have private insurance, reside in an urban area with higher terminal education, and less likely to belong to a minority group. In addition, patients with complete lymphadenectomy had to travel a longer distance to a higher-volume facility, suggesting that significant disparities still exist in the optimal oncologic management of ICC. The most important finding of the study, though, was that adequate lymphadenectomy with six or more lymph nodes resulted in improved prognostication among patients. The authors have proposed a nodal system of N0 (none positive), N1 (1–2 positive) and N2 (3 or greater positive) that is able to better discriminate survival if adequate nodes are harvested. They also introduce the concept of log-odds of lymph nodes (LODDS) calculated using the previously validated formula:  $\log_{10}(\text{number of positive lymph nodes} + 0.5 / \text{number of negative lymph nodes} + 0.5)$ . Both systems were able to better stratify survival in this cohort, however they still need prospective validation.

Opponents of routine or adequate lymphadenectomy typically cite the lack of therapeutic benefit or, in the case of ICC, the fact that it does not select patients for additional treatment since adjuvant therapy is recommended

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regardless. Other suggested barriers are the increase in operative time required and potential for complications including bile duct ischemia with lymphadenectomy. Prior to 2019, adjuvant therapy was not recommended despite meta-analyses that suggested a benefit in margin or lymph node positive disease.<sup>2</sup> In addition, lymphadenectomy continues to be indicated in the other biliary tract cancers (BTCs) including extrahepatic cholangiocarcinoma (hilar and distal) and gallbladder cancer. More recently, the updated outcomes of BILCAP demonstrated a sustained improvement in overall survival with the addition of capecitabine following resection of biliary tract cancer.<sup>3</sup> It is important to note that, because this trial included all BTC (with distal cholangiocarcinoma being the most prevalent tumor site, accounting for 33% of the study population), it is hard to extrapolate results pertaining to ICC alone. In fact, lymphadenectomy was not mandated in this trial for ICC as it began accrual in 2006 so the true estimate of nodal disease is unknown. The trial was also not powered to detect any subgroup differences between lymph node negative or positive patients for all sites. Interestingly, the recently presented STAMP trial tried to escalate adjuvant therapy with gemcitabine and cisplatin instead of capecitabine in resected, node positive extrahepatic cholangiocarcinoma, but there was no improvement in OS observed with the doublet regimen.<sup>4</sup> However, we do not have results for ICC alone.

Another factor to consider in regard to lymphadenectomy is lymph node location. While traditionally stations 8 and 12 comprised a routine portal lymphadenectomy, the AHPBA expert consensus panel recommends tailoring the lymph node harvest to tumor sidedness based on the Japanese Liver Cancer Study Group guidelines.<sup>5</sup> They include stations 1, 3, 7 along the left gastric and esophagus for left-sided ICC and station 13 behind the pancreas for right-sided lesions. Furthermore, some surgeons sample the aortocaval space (station 16) as involvement at this level represents more advanced disease outside the regional basin for any tumor. Since only the number but not location of lymph nodes is recorded in the NCDB, it is difficult to discern the impact of lymphadenectomy geography in the current study.

As neoadjuvant therapy is being considered more often in ICC, it will be important to determine its indications and effect on nodal disease. Neoadjuvant chemotherapy was administered to only 12.5% of the present cohort. The first prospective, feasibility single-arm trial accrued 30 ICC patients with resectable but oncologically high-risk patients including those with suspected or involved portal nodes to preoperative gemcitabine, cisplatin, and nab-paclitaxel (GAP) prior to resection.<sup>6</sup> A partial response rate of 23% and disease control rate of 90% were observed, with 22 of 30 patients undergoing curative-intent surgery without

added complications from the chemotherapy. All patients had a lymphadenectomy performed, with 73% R0 resection rate and 64% of patients with N0 disease. This is consistent with previous retrospective reports of a roughly 30% lymph node positive rate in ICC.

The most promising developments in ICC have been the discovery of several actionable mutations that have been predominantly been examined in the advanced setting through molecular profiling. Common alterations in IDH1 and FGFR2 have resulted in the development of targeted inhibitors all approved by the FDA within the last couple of years in the second-line setting. Little is known about the expression of these markers in the resectable space or how they may affect surgical and/or locoregional therapy. Given that more liver-directed treatments such as hepatic artery infusion pump (HAIP) and radioembolization with Y90 are being employed for localized disease, the correlation of lymph node positive disease with molecular profiles may predict the optimal treatment strategy. An example of this targeted approach was reported in a retrospective study looking at the difference of resection versus HAIP alone in patients with ICC.<sup>7</sup> For lymph node negative patients, surgical resection was associated with the best survival. However, survival in N1 patients treated with HAIP was equivalent to resection. This was also the case when examining patients who harbored an IDH1/2 mutation that appeared to be prognostic of survival only in the lymph node negative setting. Those with high-risk mutations and N1 disease had the worst prognosis regardless of therapeutic modality. Since preoperative determination of positive lymph nodes can be challenging by imaging, particularly in patients with known liver disease, it is imperative that consideration be given to perform a lymphadenectomy in patients selected for surgery. Those with suspected N1 disease may be deemed candidates for preoperative treatment with cytotoxic chemotherapy or targeted therapy. The cholangiocarcinoma community is awaiting the results of the European ACTICCA-1 trial (NCT02170090) comparing adjuvant gemcitabine/cisplatin versus capecitabine that is nearing accrual. Along with the growing enthusiasm for molecular profiling, we hope to correlate these findings in earlier stage disease by collecting this disease- and patient-specific information. Given the rarity of ICC, it is unlikely a prospective, randomized trial on lymphadenectomy will be feasible. Therefore, in the absence of a clear contraindication, we suggest that lymph nodes should be collected for proper ICC staging, prognosis, and perhaps, in the near future, treatment sequencing. So yes, similar to other cancers in the gastrointestinal tract, they do matter.

**DISCLOSURE** The author declares no conflicts of interest.

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