Intrahepatic Cholangiocarcinoma: Prognosis of Patients Who Did Not Undergo Lymphadenectomy

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BACKGROUND: The role of routine lymphadenectomy (LD) among patients undergoing surgery for intrahepatic cholangiocarcinoma (ICC) remains poorly defined. This study aimed to evaluate the role of routine LD as well as to quantify the impact of not assessing nodal station on disease-specific survival (DSS) among patients undergoing liver surgery for ICC.

STUDY DESIGN: Using data from 12 major hepatobiliary centers, 561 patients undergoing liver surgery for ICC between 1990 and 2012 were identified. The association between nodal status and DSS was assessed using Cox proportional and Aalen's linear hazards models.

RESULTS: Among the 272 (48.5%) patients who underwent LD, 123 (45.2%) had lymph node metastasis (N1). Although differences in DSS were noted between N0 and Nx patients within the first 18 months after surgery (DSS at 18 months: N0 vs Nx, 70.2% vs 60.6%, respectively, $p = 0.019$) among patients who had survived to 18 months, the DSS at 60 months of Nx patients was comparable to that of N0 patients ($p = 0.48$). Conversely, although the DSS of N1 and Nx patients was comparable in the short-term (DSS at 18 months: $p = 0.13$), among patients who had survived to 18 months, N1 patients had a lower DSS compared with Nx patients (DSS at 60 months among patients who had survived to 18 months: N1 vs Nx, 15.2% vs 45.8%, respectively, $p < 0.001$; all p values were based on the log-rank test comparing 2 survival curves).

CONCLUSIONS: Although Nx patients and N1 patients had comparable DSS in the short-term, Nx patients who survived past 18 months had a survival comparable to that of N0 patients. Lack of nodal staging may lead to heterogeneous and potentially incorrect prognostic classification of patients with ICC. (J Am Coll Surg 2015;221:1031−1040. © 2015 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved)

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Cholangiocarcinoma represents a heterogeneous group of aggressive malignancies arising from the biliary tree.[1,2] Distinguished by anatomic location, cholangiocarcinoma can be classified as intrahepatic, perihilar, or distal.[1-4] Although the annual incidence of intrahepatic cholangiocarcinoma (ICC) remains low, during recent decades, there has been a dramatic rise in the incidence of ICC from 0.32 per 100,000 in 1975 to 1 per 100,000 in 2000, making it the second most common primary liver cancer.[5,6] Although surgery remains the sole option for potential cure, only 30% to 40% of patients present with resectable disease at diagnosis.[1] High recurrence rates and poorly defined adjuvant regimens have further resulted in poor 5-year overall survival (OS) ranging from 14% to 40%.[7,8] Various studies have identified

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Abbreviations and Acronyms

AJCC = American Joint Committee on Cancer
CS = conditional survival
DSS = disease-specific survival
HR = hazard ratio
ICC = intrahepatic cholangiocarcinoma
IQR = interquartile range
LD = lymphadenectomy
OS = overall survival

patient and disease characteristics such as age at diagnosis, number of tumors, tumor size, cirrhosis, and invasion of adjacent structures to be predictive of poor overall survival.[5-7,9,10]

More recently, several reports have identified nodal status as a potentially useful prognostic indicator for ICC.[7,10-12] For example, a recent meta-analysis noted that OS varied from almost 0% among patients with lymph node metastasis to more than 45% among patients without lymph node metastasis.[10] Although guidelines recommend removal of clinically suspicious lymph nodes, the role of routine lymphadenectomy (LD) remains controversial and at best, poorly defined.[1,8,12,13] For example, in contrast to the practices of Japanese centers, LD is not routinely performed at many Western centers.[1,11] Noting that LD may not be necessary among patients with ICC, Shimada and colleagues[13] reported no improvements in survival or recurrence among patients who underwent LD. In contrast, De Jong and associates[8] demonstrated that among patients who underwent routine LD, nearly one-third had lymph node metastasis and a worse median survival. Furthermore, the authors reported that among patients with lymph node metastasis, other established risk factors such as tumor size, number, and invasion did not discriminate prognosis. In turn, the investigators noted that LD should be routinely performed for ICC to facilitate risk stratification and more appropriate management.

Given these large variations in practices of LD for ICC, as well as disparate data pertaining to the influence of LD on prognosis, the objective of this study was to characterize the role of LD among patients undergoing surgery for management of ICC. Specifically, using a large multi-institutional cohort of patients, we sought to determine the prognosis of patients with N0 vs N1 disease, as well as to quantify the impact of not assessing nodal station on disease-specific survival (DSS) among patients undergoing liver surgery for management of ICC.

METHODS

Data sources and study population

Data for patients with histologically confirmed ICC were abstracted from an international multi-institutional database of 617 patients who underwent liver surgery between 1990 and 2013 at 12 major hepato-biliary centers (Johns Hopkins Hospital, Baltimore, MD; Medical College of Wisconsin, Milwaukee, WI; Stanford University, Palo Alto, CA; University of Virginia, Charlottesville, VA; Emory University, Atlanta, GA; University of Pittsburgh, Pittsburgh, PA; Fundeni Clinical Institute of Digestive Disease, Bucharest, Romania; Curry Cabral Hospital, Lisbon, Portugal; Hopitaux Universitaires De Geneve, Geneva, Switzerland; Ospedale San Raffaele, Milan, Italy; University of Sydney, Sydney, Australia; and Eastern Hepatobiliary Surgery Hospital, Shanghai, China). Patients presenting with metastatic disease at the time of diagnosis (American Joint Committee on Cancer [AJCC] stage M1) were excluded from the cohort. Similarly, patients who underwent a palliative resection or patients treated via percutaneous ablation were excluded from the study population.

In addition to baseline demographic data including age and sex, pathologic tumor characteristics were collected for each patient. Specifically, these data included tumor location, tumor size, number of lesions, morphologic sub-type, lymph nodes harvested, number of metastatic lymph nodes, and tumor invasion (perineural and vascular). Tumor size was defined as the largest diameter (in cm) for the tumor within the resected specimen. When multiple tumors were resected, the largest measured diameter was used to define tumor size. Similarly, histologic grade was defined as either well, moderately, or poorly differentiated, with the highest histologic grade used to define tumor grade among patients with multiple resected specimens. In addition, information on surgery, receipt of lymphadenectomy, radiation, or chemotherapy was also collected for each patient. Margin and nodal status were determined from the final postoperative pathologic report.

Statistical analysis

Continuous variables are summarized as medians with interquartile ranges (IQR); categorical variables are reported as whole numbers and percentages. Categorical variables were compared using the Fisher's exact test and continuous variables using the Mann-Whitney U test.

The primary outcome was DSS, defined as the time interval between the date of surgery and the date of death, when the cause of death was related to ICC. Time was