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Original Article

Evaluation of prognostic factors and implication of lymph node dissection in intrahepatic cholangiocarcinoma: 10-year experience at a tertiary referral center

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Abstract

Background: Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver malignancy, and surgical resection remains the only potentially curative treatment. However, the existing literature indicates that those prognostic factors associated with outcome after surgery remain poorly defined.

Methods: Data were retrospectively collected from 103 patients with ICC who underwent surgical resection between 2005 and 2014. The patients were divided into two groups: one with (D1) and one without (D0) lymph node dissection of hepatic hilum according to the surgery performed. Thereafter, the prognostic values of clinicopathological characteristics were evaluated.

Results: The median overall survival (OS) after surgical resection of ICC was 43.9 months [95% confidence interval (CI), 11.6−76.2 months]. The 1-, 3-, and 5-year OS rates were 85.5%, 52.8%, and 45.6%, respectively. Multivariable analysis showed that lymph node metastases [hazard ratio (HR), 6.70; 95% CI, 2.18−20.55], positive resection margins (HR, 2.67; 95% CI, 1.14−6.23), periductal infiltration (HR, 3.64; 95% CI, 1.27−10.44), and poor differentiation (HR, 2.90; 95% CI, 1.41−5.95) were independently associated with poor survival. There were no significant differences in clinicopathological characteristics between D1 and D0 groups, except for vascular invasion ($p = 0.018$) and perineural invasion ($p = 0.008$). In the D1 group, lymph node metastases were associated with late T stages, multiple tumors, and elevated serum carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) levels.

Conclusion: Regional lymph node metastasis, positive resection margin, periductal infiltration, and poor differentiation were poor prognostic factors in patients with ICC after curative surgery. Lymph node dissection did not show survival benefits, but was useful for nodal staging. However, lymph node metastases were strongly associated with late T stages, multiple tumors, and elevated serum CEA and CA19-9 levels.

Keywords: cholangiocarcinoma; lymph node dissection; prognostic factors

Conflicts of interest: The authors declare that they have conflicts of interest related to the subject matter or materials discussed in this article.

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1. Introduction

Intrahepatic cholangiocarcinoma (ICC) originates from either the small intrahepatic ductules, or the large intrahepatic ducts proximal to the bifurcation of the right and left hepatic ducts. ICC accounts for 10−15% of all liver cancers, and is the second most common primary malignancy of the liver after hepatocellular carcinoma.[1,2] Surgical resection remains the only potentially curative treatment for ICC. However, only 30−40% of patients present with resectable disease at the time of diagnosis.[3] High recurrence rates have contributed to a poor 5-year survival, which ranges from 14% to 40%.[4,5] Recently, a multicenter international study of ICC patients reported a median postoperative overall survival (OS) of only 14.8 months.[6] Accurate staging may therefore be helpful to select suitable patients to undergo surgery or receive earlier chemotherapy.

The 6th edition of the American Joint Committee on Cancer (AJCC) cancer staging system did not separate ICC from hepatocellular carcinoma, whereas the staging system referenced in the 7th edition of the AJCC introduced a separate TNM (tumor, node, metastasis) classification for ICC.[7] The latest classification focuses on multiple tumors, vascular invasion, and lymph node metastases. However, several studies found additional prognostic factors, including age, positive surgical margins, tumor sizes, and tumor differentiation.[4,8,9] Prognostic nomograms, including additional factors, might be more accurate than the conventional AJCC staging system for predicting outcomes.[10] In this study, we analyzed 103 ICC patients who received surgical resection with curative intent at the Taipei Veterans General Hospital in Taiwan. We aimed to identify additional prognostic factors and evaluate the effect of lymph node dissection (LND) on prognosis in this cohort of ICC patients.

2. Methods

2.1. Patients and collection of clinicopathological data

This study enrolled a total of 103 patients with ICC who received surgical resection with curative intent at the Taipei Veterans General Hospital, Taiwan, between April 1, 2005 and December 31, 2014. The study was approved by the Institutional Review Board of this hospital. Patients were evaluated by recording the baseline history, physical examination, serum laboratory tests, and appropriate imaging studies [e.g., computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen and pelvis and radiography or CT of the chest] at the discretion of the treating surgeon. A diagnosis of ICC was confirmed by pathologic evaluation of the resected specimen. LND of hepatic hilum was performed at the discretion of the surgeon, based on preoperative imaging and intraoperative findings. Patients were divided into two groups: one with LND of the liver hilum (D1) and one without (D0). The LND was performed by dissecting along the hepatoduodenal ligament and removing the lymph nodes. For surgical margin status, R0 was defined as free surgical cut margin without residual tumor cell microscopically. R1 resection was defined as unclear surgical margin with residual tumor cells observed only under microscopic examination. R2 resection was defined as incomplete tumor resection with grossly residual tumor on surgical cut surface. The pathologic sides were reviewed by a single pathologist (Y.C. Yeh), and the pathological factors—including tumor numbers, tumor sizes, resection margins, nodal status, tumor-growth types, tumor differentiation, vascular invasion, and perineural invasion were reevaluated. Tumors were restaged using the 7th edition of the AJCC TNM classification according to each patient's pathological review. Patients with combined hepatocellular−cholangiocarcinoma were excluded.

2.2. Follow-up study

After surgery, all patients were followed up routinely in our clinics. The follow-up evaluation included a physical examination and blood chemistry tests at each visit, as well as measurement of serum levels of carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9). The remnant livers were examined by ultrasound every 3 months. CT of the abdomen or magnetic resonance cholangiopancreatography were performed when a new lesion was detected by ultrasound, or when elevated levels of CEA or CA19-9 were noted. Moreover, when patients complained of bone pain, whole body bone scans were performed to detect bone metastases. If any of the abovementioned follow-up mechanisms indicated recurrences, the patient received a more comprehensive assessment, including angiographic evaluation. The date of the last follow-up, death, and recurrence were recorded for all patients. Recurrences or metastases of ICC were defined as the appearance of newly detected tumors with typical radiologic features on CT, MRI, or positron emission tomography scan, or with pathological confirmation by tissue biopsy. The OS time was defined as the interval between the date of surgery and either the date of death or the date of the last follow-up. The disease-free survival time was defined as the interval between the date of surgery and the date of recurrence.

2.3. Statistical analysis

Demographic and clinicopathologic characteristics were described as summary statistics obtained using established methods and were presented as percentages or median values. Univariate survival curves were estimated using the Kaplan−Meier method, and compared by means of the log-rank test. Continuous variables, such as serum concentration of total bilirubin and sizes (diameter) of the tumor, were transformed into binary categorical variables. For continuous variables, the cutoff point showing the lowest p value was retained if the value reached significance. Variables that were statistically significant as predictors were further analyzed using a multivariate Cox proportional hazards regression model, except for cases involving missing data that comprised a variable in >10% of cases. The chi-square test was applied to compare differences in demographic and clinicopathologic characteristics between the two groups of patients with

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