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ORIGINAL ARTICLE

The prognostic importance of lymphovascular invasion in cholangiocarcinoma above the cystic duct: a new selection criterion for adjuvant therapy?

Sameer H. Patel[1], David A. Kooby[1], Charles A. Staley III[1], Juan M. Sarmiento[2] & Shishir K. Maithel[1]

[1]Division of Surgical Oncology, Department of Surgery, Winship Cancer Institute, and [2]Division of General Surgery, Department of Surgery, Emory University, Atlanta, GA, USA

Abstract

Objective: Criteria for selecting patients to receive adjuvant chemotherapy in cases of resected intrahepatic or hilar cholangiocarcinoma (CC) are lacking. Some clinicians advocate the provision of adjuvant therapy in patients with lymph node (LN)-positive disease; however, nodal assessment is often inadequate. The aim of this study was to identify a surrogate criterion based on primary tumour characteristics.

Methods: All patients who underwent resection for hilar or intrahepatic CC at a single institution between January 2000 and September 2009 were identified from a prospectively maintained database. Pathological factors were recorded. The primary outcome assessed was overall survival (OS).

Results: In total, 69 patients underwent resection for hilar (n = 34) or intrahepatic (n = 35) CC. Their median age was 66 years and 27 patients (39%) were male. Median follow-up was 22 months and median OS was 17 months. Median tumour size was 5 cm. Overall, 23% of patients had a positive resection margin, 44% had perineural invasion, 32% had lymphovascular invasion (LVI) and 25% had positive LNs. The median number of LNs removed was two and the median number of positive LNs was zero. The presence of LVI was associated with reduced OS (11.9 months vs. 23.1 months; P = 0.023). After accounting for all other adverse tumour factors, the presence of LVI persisted as the only negative prognostic factor for OS on multivariate Cox regression.

Conclusions: In patients who had undergone resection of hilar or intrahepatic CC, the presence of LVI was strongly associated with reduced OS. Thus the finding of LVI may potentially be used as a criterion in the selection of patients for adjuvant chemotherapy.

Keywords

resection < intrahepatic cholangiocarcinoma, chemotherapy < hilar cholangiocarcinoma, pathology

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Correspondence

Shishir K. Maithel, Division of Surgical Oncology, Department of Surgery, Winship Cancer Institute, Emory University, Second Floor, 1365C Clifton Road Northeast, Atlanta, GA 30322, USA. Tel: + 1 404 778 5777. Fax: + 1 404 778 4255. E-mail: smaithe@emory.edu

Introduction

Cholangiocarcinoma (CC) is an uncommon malignancy that affects approximately 5000 individuals per year in the USA.[1] Although CC is a rare tumour, it is the second most common primary hepatic malignancy after hepatocellular carcinoma and globally accounts for 3% of all gastrointestinal malignancies.[2] Because of its aggressive behaviour and modest response to current chemotherapy regimens, longterm survival is poor and tumour incidence nearly equals mortality rates.

Cholangiocarcinomas are divided into three general categories based on their anatomic location of origin. Intrahepatic CC

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arises from within the hepatic parenchyma and accounts for approximately 20% of all CCs; the incidence of this category seems to be on the rise.[3,4] Hilar CCs are the most common form (50–60%) and occur at the confluence of the hepatic ducts; the remaining 20–30% of CCs are categorized as distal CCs and often arise from within the intrapancreatic portion of the common bile duct.[3] Complete resection remains the mainstay of therapy and represents the only opportunity for cure. Unfortunately, nearly 75% of patients present with unresectable disease, for which chemotherapy offers a median survival of only 5–8 months.[5,6] In patients with resectable disease, however, 5-year survival rates remain at only 35–45%.[7] Efforts to improve survival have included the administration of adjuvant chemotherapy, but this has met with limited success and its potential effectiveness is likely to be largely dependent on appropriate patient selection. Based on the recent Advanced Biliary Cancer (ABC-02) Trial, a doublet chemotherapy regimen consisting of gemcitabine (Gem) with concurrent cisplatin (Cis) has emerged as the standard of care for advanced CC as patients receiving this therapy showed improved median overall survival (OS) compared with those who received Gem monotherapy (11.7 months vs. 8.1 months; $P < 0.001$).[8] Currently, there are minimal data to guide the use of adjuvant chemotherapy after complete resection, especially as previous regimens were marginally effective and have not been shown to be beneficial in the adjuvant setting.[9,10] The ABC-02 Trial provides us with a new and more effective regimen (Gem/Cis) that may potentially be utilized also after resection. Selection criteria, however, for offering chemotherapy after resection are not standardized for CC.

Many studies have investigated prognostic factors associated with poor survival after resection of CC. One of the key pathological factors consistently associated with poor survival is lymph node (LN)-positive disease.[11–13] The American Joint Committee on Cancer (AJCC) utilizes LN involvement in addition to vascular invasion, presence of multiple tumours and metastatic disease for the staging of intrahepatic CC.[14] Lymph node-positive disease is frequently used as a selection criterion for adjuvant chemotherapy. Similarly, several studies have found LN-positive disease to be a poor prognostic factor for survival in patients with hilar CC.[15–17] Although the current classification system does provide some information with regard to LN involvement and longterm prognosis, there is no standard guideline for the number of nodes that must be retrieved to ensure accurate staging, probably because the porta hepatis typically harbours very few LNs. Furthermore, portal lymphadenectomy (LAD) is not routinely performed for intrahepatic CC. Thus, the median number of LNs retrieved during resection of hilar or intrahepatic CC is often minimal to none. The aim of this study was to identify a surrogate marker for adverse tumour biology based on the primary tumour that might be used as an alternative criterion in the selection of patients for adjuvant chemotherapy.

Materials and methods

A prospectively maintained hepatobiliary surgery database at the Winship Cancer Institute at Emory University was reviewed for all patients with a diagnosis of intrahepatic or hilar CC who underwent resection between January 2000 and September 2009. Patients with advanced disease or those diagnosed with distal CC were excluded from analysis. Permission from Emory University's Institutional Review Board was obtained prior to data review, and Health Insurance Portability and Accountability Act (HIPAA) compliance was ensured.

A total of 69 patients who underwent resection were identified. Overall survival was ascertained using the clinical follow-up data documented in each patient's medical record and the Social Security Death Index. Pathology reports were reviewed for important tumour factors that are known to have prognostic value for patient survival. Specifically, data on tumour size, number, margin status, LN involvement, presence of lymphovascular invasion (LVI) and perineural invasion (PNI) were recorded.[11,18,19]

Statistical analysis

Data were analysed using SPSS Version 17.0 for Windows (SPSS, Inc., Chicago, IL, USA). Kaplan–Meier log-rank survival analysis was used to determine the association of each pathological factor with patient survival. Multivariate Cox regression analysis of adverse tumour factors was performed to determine which pathological variables were independently associated with decreased OS.

Results

Clinicopathological variables and postoperative outcomes are shown in Table 1. The median number of LNs retrieved was three (range: 0–24) in hilar CC and one (range: 0–10) in intrahepatic CC ($P = 0.004$). There was no statistical difference in the frequency of LN positivity between hilar and intrahepatic CC patients (32% vs. 17%, respectively; $P = 0.17$). The median number of positive LNs in both hilar and intrahepatic CC was zero (hilar: range 0–3; intrahepatic: range 0–2; $P = 0.146$).

Survival analysis

The median length of follow-up for survivors was 22 months (range: 0.5–81.4 months). At the time of last follow-up, 46 patients (67%) had died. Median OS for all patients was 17.3 months (range: 0.3–81.4 months). Kaplan–Meier survival analysis of known prognostic factors revealed the presence of LVI to be the only adverse pathological factor significantly associated with reduced survival (Fig. 1A–E). A subset analysis of only those patients with LN-negative disease or those in whom no LNs were assessed ($n = 52$) demonstrated a strong trend towards reduced survival in patients whose tumours were positive for LVI (Fig. 2). Tumour grade was not statistically associated with poor survival (median OS: well, 28.3 months; moderate, 20.3 months; poor, 14.4