ORIGINAL ARTICLE

Mixed hepatocellular and cholangiocarcinoma: a rare tumor with a mix of parent phenotypic characteristics

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Abstract

Background: Intrahepatic lesions of mixed hepatocellular (HCC) and intrahepatic cholangiocellular carcinoma (ICC) histology are rare. The aim was to describe the natural history of these tumors relative to monomorphic ICC or HCC utilizing the National Cancer Data Base (NCDB).

Methods: Patients with ICC, HCC, and mixed histology (cHCC-CCA) were identified in the NCDB (2004–2012). Inter-group comparisons were made. Kaplan–Meier and multivariable Cox Proportional Hazards analyzed overall survival.

Results: The query identified 90,499 patients with HCC; 14,463 with ICC; and 1141 with cHCC-CCA histology. Patients with cHCC-CCA histology were relatively young (61 vs. 62 (HCC, $p = 0.877$) and 67 (ICC, $p < 0.001$) years) and more likely to have poorly differentiated tumor (29.2% vs. 10.3% (HCC) and 17.2% (ICC) $p < 0.001$). Median overall survival for cHCC-CCA was 7.9 months vs. 10.8 (HCC) and 8.2 (ICC, all $p < 0.001$). Stage-specific survival for mixed histology tumors was most similar to that of HCC for all stages. cHCC-CCA were transplanted at a relatively high rate, and transplant outcomes for mixed tumors were substantially worse than for HCC lesions.

Discussion: cHCC-CCA demonstrate stage-specific survival similar to HCC, but post-surgical survival more consistent with ICC. Patients with a pre-operative diagnosis of cHCC-CCA should undergo resection when appropriate.

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Introduction

Combined hepatocellular and cholangiocarcinoma (cHCC-CCA) is a rare tumor with poor prognosis that arises in the liver. This entity is described as demonstrating histologic features of both the hepatocellular (HCC) and intrahepatic cholangiocarcinoma (ICC) components which comprise it. It is a clinical conundrum due to behavior being a mixture of its components.[1] Classifications for these tumors include the Allen & Lisa classification[2] and the Goodman classification.[3] These pathologic classifications define a spectrum ranging from independent occurrence of both tumor histologies in the same liver to mingling tumors and a distinct subtype resembling fibrolamellar HCC histology. The diagnosis of cHCC-ICC is usually made at pathologic evaluation after either resection or transplantation, and the pre-operative likelihood of identifying a mixed-histology tumor is low.

The largest series suggests that cHCC-CCA represent less than 1% of all primary hepatic malignancies.[4–7] Most literature on this topic is descriptive in nature, consisting of case reports and small series. Consequently, data regarding surgical outcomes for cHCC-CCA are limited. Staging criteria for these tumors are

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Abbreviations: ICC, intrahepatic cholangiocarcinoma; HCC, hepatocellular carcinoma; cHCC-CCA, combined hepatocellular and intrahepatic cholangiocarcinoma; NCDB, National Cancer Data Base; PUF, participant user file; AJCC, American Joint Committee on Cancer; CoC, Commission on Cancer; ACS, American College of Surgeons; SEER, surveillance epidemiology and end results; US, United States.

particularly controversial, and due to their mixture of phenotypic characteristics it is unclear whether they should be treated more like HCC or ICC. Currently, clinical consensus opposes the use of transplantation as a therapeutic option for patients with these tumors.[8–10] However, data regarding optimum management of cHCC-ICC remain murky.

This project sought to improve understanding of this topic by comparing the survival of these patients to patients with isolated HCC and ICC. In order to thoroughly investigate this question, the National Cancer Data Base – a national hospital-based datasource in the United States (US) – was utilized.[2,3]

Methods

This retrospective review was based on the National Cancer Data Base (NCDB) participant user file (PUF) from 1998 to 2011. The query was focused on 3 patient cohorts: those with (1) intrahepatic cholangiocarcinoma (ICC), (2) hepatocellular carcinoma (HCC), and (3) biphenotypic cHCC-CCA mixed morphology tumors. The Mayo Clinic Institutional Review Board has deemed analysis of the NCDB PUF exempt from review. The NCDB contains over 30 million records of individual cancer patients collected by more than 1500 Commission on Cancer (CoC) approved facilities across the US. The NCDB is estimated to capture approximately 70% of all newly diagnosed patients of cancer in the US.[11]

Patients were identified using International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) topography (C22.0–22.1) and histology codes (8170–8175 for HCC, 8160–8162 for ICC, and 8180 for cHCC-CCA). Curative intent surgery included surgery of primary site codes 20–26 – wedge resection; 30–38 – Lobectomy; 50–59 extended lobectomy; 60–61 hepatectomy; 65–66 – bile duct excision; and 75 – hepatectomy with transplantation. Patients with surgical codes 0 (no surgery), 10–17 (local tumor destruction), 90 (Surgery, NOS), and 99 (Unknown) were classified as not having curative intent surgery. Only patients who were diagnosed and treated at the performing facility were included. Pathologic TNM staging information is recorded in the NCDB PUF using the American Joint Commission on Cancer (AJCC) 6th and 7th edition staging manuals dependent on year of diagnosis, and the AJCC summary stage variable was used for staging purposes. Patients who developed cancer at more than one site in their lifetime were excluded as were patients with missing follow up or final pathological staging data. Fibrosis was not assessed due to large amounts of missing data on this parameter within the database.

Statistical analysis

For inter-group comparisons, normally distributed continuous data were expressed as mean and standard deviation and examined with the two-tailed student's t-test. Non-normally distributed continuous data were expressed as median with inter-quartile range and were examined with the Mann–Whitney U test. The Pearson's chi-squared was used to examine uniformly distributed categorical variables and Fisher's exact test was used for categorical variables with non-uniform distribution. Missing data were handled with indicator variables as shown in the tables.

Survival analysis was performed using the method of Kaplan and Meier with survival defined as time from diagnosis to death or censor. Survival curves were compared with the log-rank test. NCDB neither provides data on recurrence nor cause of death; therefore overall survival was the primary outcome. To estimate the independent effect on survival, a multivariable Cox proportional hazards model was developed which included age, race, comorbidity score, tumor size, node status (N0/N1), lymphovascular invasion, tumor grade (high/low), pathologic stage (localized/locally advanced/metastatic), CA 19-9 elevation, positive margins, chemotherapy, radiotherapy and surgical intervention (none/local/resection/transplant). A p value <0.05 was considered statistically significant for all comparisons. Statistical analysis was performed with R version 3.2.2 (R Foundation for Statistical Computing – Vienna, Austria www.r-project.org).

Results

The query identified in total 106,103 patients, including 90,499 (85%) patients with HCC, 14,463 (14%) with ICC, and 1141 (1%) with mixed histology. Patients with mixed histology were of similar median [IQR] age compared with HCC (61 [54–71] vs. 62 [53–71] years) but younger than those with ICC (67 [57–76] years $p < 0.001$). cHCC-ICC and HCC were found more often in male patients, but ICC had approximately equivalent gender distribution. ICC had the greatest prevalence among Caucasian patients (83.8%) whereas cHCC-ICC and HCC had greater prevalence among African Americans (12.4% and 15.4% respectively). The proportion of patients with high comorbidity scores (19.2% with two or more comorbidities – Table 1) was greatest in patients with HCC.

cHCC-ICC had the highest proportion of very large tumors (15.9% > 10 cm). cHCC-ICC and ICC had approximately equal likelihood of node harvests and both were greater than HCC. The rate of node positivity was greatest among patients with ICC (36.8% vs. 19.7% for mixed and 6.5% of HCC lesions). Patients with cHCC-ICC lesions were less likely than those with ICC to have elevated carbohydrate antigen 19-9 (CA 19-9 elevated in 46.0% vs. 66.3%, $p < 0.001$). cHCC-ICC had the highest frequency of poorly differentiated tumor (29.2% vs. 10.3% (HCC) and 17.2% (ICC), $p < 0.001$). Stage IV disease was more frequent with ICC than either HCC or cHCC-ICC (35.7% vs. 22.4% and 29.5% respectively, both $p < 0.001$ – Table 1). The rate of margin positive resections was greatest for ICC (19.1% vs. 5.8% for cHCC-ICC and 4.8% for HCC – Table 1).

Interestingly liver transplantation was employed more frequently for patients with cHCC-CCA than either ICC or