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HEPATIC CANCER (A SINGAL AND A MUFTI, SECTION EDITORS)

Management of Combined Hepatocellular Carcinoma-Cholangiocarcinoma

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Abstract

Purpose of Review To review the recent consensus on the nomenclature, clinical features, diagnosis, and treatment of combined hepatocellular carcinoma-cholangiocarcinoma (cHCC-CCA).

Recent Findings cHCC-CCA is a primary liver carcinoma with varying degrees of hepatocytic and cholangiocytic cytology and architecture within the same tumor. The diagnosis of cHCC-CCA can only be established based on histologic examination. Surgical resection should be considered in patients with resectable tumors who do not have underlying liver disease or clinically significant portal hypertension. While treatment by liver transplantation (LT) is controversial due to the high risk of post-LT recurrence, LT should remain as a potentially curative option in a highly selected group of patients. Little data exist for the outcome of other treatments.

Summary High-quality multicenter prospective studies should be conducted to better understand this rare but increasingly recognized tumor.

Keywords Mixed tumor · Hepatocholangiocarcinoma · Hepatocellular cholangiocarcinoma · Biphenotypic tumor · Treatment

Introduction

Combined hepatocellular carcinoma-cholangiocarcinoma (cHCC-CCA) is a primary liver malignancy with hepatocytic and cholangiocytic differentiation in a single tumor nodule [1••]. This tumor has been named as mixed hepatocellular cholangiocarcinoma, hepatobiliary carcinoma, biphenotypic primary liver carcinoma, combined hepatocellular cholangiocarcinoma, cholangiocellular carcinoma, hepatocellular carcinoma with dual phenotype etc. As knowledge of the histologic and molecular pathology of cHCC-CCA accumulates, primary liver cancers sharing characteristics of both HCC and CCA have been recognized increasingly more frequently [2, 3, 4•]. In this article, we discuss a recently published consensus statement on the nomenclature, and review the clinical presentation, diagnosis, and treatment of cHCC-CCA.

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Definition

cHCC-CCA has been defined using a number of different criteria, which has led to under-recognition and under-diagnosis. Consequently, this subtype of primary liver carcinoma has not received the attention of clinicians and medical researchers commensurate with its incidence. In order to standardize the nomenclature of this tumor, an international group of experts recently published a consensus guideline with the aim of creating uniformity of histologic diagnosis and facilitating scientific studies [1••]. The expert panel defined cHCC-CCA as "primary liver carcinoma with varying degrees of hepatocytic and cholangiocytic cytology and architectures, either mixed or as separate areas within the same tumors" [1••]. The expert panel concluded that distinct multifocal HCC and CCA in separate nodules, collision tumors of HCC and CCA arising separately in the same liver, morphologically typical HCC with only immunohistochemical expression of cholangiocytic or stem/progenitor cell markers, and morphologically typical CCA with only immunohistochemical expression of hepatocytic or stem/progenitor cell markers should not be considered as cHCC-CCA. Double primary of HCC and CCA is the recommended terminology when the hepatocellular carcinoma component is clearly separated from the cholangiocarcinoma component by intervening non-neoplastic liver [5].

Epidemiology and Clinical Presentation of Mixed Tumor

The incidence rates of cHCC-CCA are not well known. A recent study using data from the Surveillance, Epidemiology, and End Results (SEER) registry reported that about 0.8% of primary liver cancers are cHCC-CCA [6]. Partly because of its complex morphological diversity and the lack of a consistent nomenclature, cHCC-CCA has been under-recognized and under-diagnosed. Hence, the true incidence rate of this tumor may be much higher than is currently reported in the literature. Increasing understanding of cHCC-CCA and recognition among clinicians and pathologists may lead to higher reported incidence rates of this tumor in the near future.

Clinical characteristics of patients with cHCC-CCA have been reported in several retrospective studies [7–9, 10•, 11–13]. Similar to HCC, there is a male gender predilection and mean age of diagnosis is in the late 50s and early 60s. About half of the cases occur in the absence of underlying cirrhosis. About 40–70% of patients present with elevations of serum AFP and 30–60% of patients present with elevation of serum CA 19-9. It is important to recognize that only 10–30% of patients have elevation of both tumor markers. The largest study included 1141 patients with cHCC-CCA from the National Cancer Database, which is estimated to capture approximately 70% of all newly diagnosed cancer patients in the USA [10•]. The median age at diagnosis was 62 and two thirds of the patients were male. Elevation of the CA 19-9 tumor biomarker was seen in 46% of the cases, which is less common than in intrahepatic cholangiocarcinoma (CCA) (66.3%). Lymph node positivity was more common in cHCC-CCA (18.7%) than hepatocellular carcinoma (HCC) (6.5%), but less common than in CCA (36.8%). cHCC-CCA had the highest frequency of poorly differentiated tumors (29.2% vs. 10.3% (HCC) and 17.2% (CCA), $p < 0.001$). It is important to note that most data in the literature are from surgical series as the diagnosis is typically established on pathologic review of surgically resected specimens. Non-surgical cases are often misdiagnosed as either HCC or CCA, partly due to the intra-tumoral heterogeneity of cHCC-CCA, which can only be fully assessed in the surgically resected specimen.

Diagnosis

Although there are no formal radiologic criteria for the diagnosis of cHCC-CCA, a few retrospective studies have summarized the typical radiologic features of cHCC-CCA [2, 14, 15, 16•, 17]. By multiphasic CT or dynamic MRI, cHCC-CCA often shows regions of arterial phase hyperenhancement with delayed washout, which is a specific finding of HCC. cHCC-CCA also often shows delayed central enhancement, which is a characteristic feature of CCA. When tumors show specific features of both types of cancers within the different regions of the same nodule, cHCC-CCA should be suspected. Obtaining several biopsies from areas with different radiologic features within the tumor may help in confirming the diagnosis of cHCC-CCA preoperatively, especially in the right clinical setting (e.g., atypical radiologic features of HCC with elevated CA 19-9 or atypical radiologic features of CCA with elevated AFP). Prospective correlative studies comparing pretreatment radiology images and the associated surgical pathology will be crucial next steps to define the radiologic characteristics of cHCC-CCA.

The diagnosis of cHCC-CCA can only be established based on histologic examination. Histology must show characteristic cytologic and architectural features of HCC and CCA in separate regions of a single tumor under white-light microscopic examination. Positive staining for markers of both HCC (e.g., AFP, Glypican 3) and CCA (e.g., K7, K19, cytoplasmic CD10) by immunohistochemistry is not sufficient or required for the diagnosis of cHCC-CCA. However, these findings may provide supporting evidence of cHCC-CCA [5, 18]. Figure 1 shows a representative case of resected cHCC-CCA with typical radiologic and histologic features.

Treatment of cHCC-CCA

Surgical Resection

The optimal treatment approach for cHCC-CCA is undefined. For cHCC-CCA arising in the setting of cirrhotic liver disease, treatment decisions should take into account not only the extent of tumor, but also the degree of underlying hepatic dysfunction. Similar to HCC or CCA, surgical resection should be considered in patients with resectable tumors who have compensated liver disease without clinically significant portal hypertension. There are a number of studies evaluating the clinical outcome of patients with cHCC-CCA after surgical resection, which are summarized in Table 1 [6, 7, 10•, 11, 13, 19–22]. A large retrospective study of a total of 1141 patients with cHCC-CCA using the National Cancer Data Base showed that surgical resection is performed more frequently for patients with cHCC-CCA (21.5%) than for patients with HCC (9.3%) or CCA (16.8%) ($p < 0.01$), presumably due to the lower prevalence of underlying hepatic dysfunction or biliary obstruction. The SEER analysis showed that patients diagnosed with cHCC-CCA and treated with major/minor hepatic resection had 5-year overall survival rates of 28.1%/27.1% and disease-specific survival rates of 46.5%/31.9%, respectively [6]. While post-resection survival of patients with cHCC-CCA appears to be worse than for patients with HCC, surgical resection of tumor was associated with a 71–75% risk reduction in disease-specific mortality compared to a no-surgery reference group after adjusting for other confounders including race, year of diagnosis, SEER

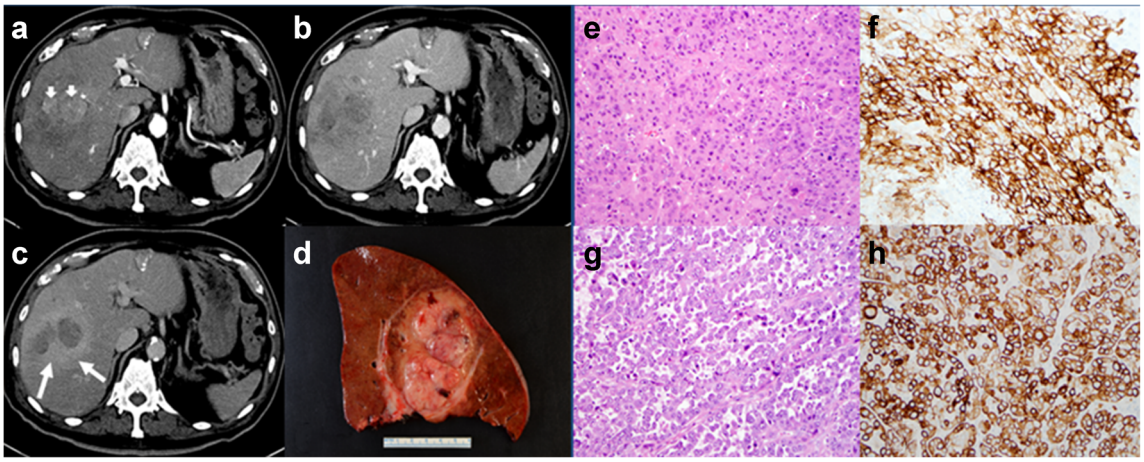

Fig. 1 Radiologic and histologic features of cHCC-CCA. 77-Year-old male with a cHCC-CCA Axial CT images in late arterial (**a**), portal venous (**b**), and delayed (**c**) phases demonstrating a heterogeneous tumor in right lobe with central nodular areas of arterial phase hyperenhancement (small white arrows) that show washout in portal venous and delayed phase suggestive of hepatocellular carcinoma. A thick and irregular rim shows mild arterial phase hyperenhancement that continues to enhance in portal venous phase and reaches maximum enhancement in delayed phase (large white arrows)—features consistent with cholangiocarcinoma. Surgical specimen photograph (**d**) showing the tumor with central nodular regions and thick irregular rim. Under microscopy, histology confirmed that tumor comprised of 20% hepatocellular carcinoma (**e**) with positive immunostaining for glypican 3 (**f**) and 80% cholangiocarcinoma (**g**) with positive immunostaining for CK7 (**h**)

tumor stage, and tumor size [6, 11]. One study showed that elevation of CA 19-9, but not elevation of AFP, was predictive of poor overall survival, suggesting that having a larger burden of phenotypic CCA than HCC elements in a tumor may be a determining factor for patient prognosis [19].

Liver Transplantation

While the therapeutic benefit of surgical resection is well established in patients with resectable disease, the role of LT in patients with cHCC-CCA is controversial [6, 20, 23–27]. As the clinical outcome of LT is superior to resection and it can be offered in patients with hepatic dysfunction, it might be an option for patients with small tumor burden in whom the degree of underlying liver dysfunction precludes surgical resection [24–26]. On the other hand, post-LT outcomes for cHCC-CCA patients are worse than for patients with HCC [6, 20, 23]. The SEER database analysis showed that patients with cHCC-CCA treated with LT had a 5-year overall survival rate of 41% and disease-specific survival rate of 53%, which are significantly better than other therapies but worse than the outcomes of patients with HCC, whose 5 year overall and disease-specific survival

Table 1 Outcome after surgical resection of cHCC-CCA

	Data source/design	Number of cases	Main outcome
Bergquist et al. [10•]	US National Cancer Data Base/retrospective	245	5-year overall survival, 30%
Garancini et al. [6]	SEER data/retrospective	81	5-year overall survival, 28%
Yoon et al. [11]	Single-center in Korea/retrospective	40	5-year overall survival, 31% 5-year recurrence-free survival, 19%
Groeschl et al. [20]	SEER data/retrospective	35	3-year overall survival, 46%
Ariizumi et al. [7]	Single-center in Japan/retrospective	33	5-year overall survival, 24% 5-year recurrent free survival, 16%
Kim et al. [19]	Single-center in Korea/retrospective	29	3-year overall survival, 37% 3-year recurrent free survival, 26%
Yano et al. [22]	Single-center in Japan/retrospective	26	5-year overall survival, 23%
Zhan et al.* [12]	Single-center in China/retrospective	25	2-year overall survival, 49% 2-year recurrent free survival, 41%
Koh et al. [13]	Single-center in Korea/retrospective	24	3-year overall survival, 47% 3-year cumulative recurrence, 63%
Jarnagin et al. [21]	Single-center in US/retrospective	21	5-year overall survival, 24%

* Outcome was analyzed in 27 cases (25 cases of resection and two cases of LT)

rates were 67% and 80%, respectively [6]. A more recent study investigated the long-term outcomes of patients undergoing LT for cHCC-CCA versus patients with HCC or CCA using the United Network for Organ Sharing (UNOS) database [23]. The overall survival rates at 1, 3, and 5 years for cHCC-CCA (82%, 47%, and 40%) were similar to the survival rates for CCA (79%, 58%, and 47%), but significantly worse than for HCC (86%, 72%, and 62%, $p = 0.002$). A recent retrospective single-center study performed a propensity-matched analysis of patients with cHCC-CCA undergoing LT [25]. This study included 12 patients with cHCC-CCA who were matched 1:3 to patients with HCC on both pre-transplant and explant tumor characteristics. The two groups had similar 5-year recurrence-free survival (42% vs 44%, $p = 0.45$). None of the cHCC-CCA patients with well- or moderately differentiated tumors developed a recurrence. The authors concluded that patients with well- or moderately differentiated cHCC-CCA and small tumor burden have excellent survival with a low-risk for post-LT recurrence and should not be excluded from LT although pre-transplant histologic diagnosis of cHCC-CCA will be difficult given intra-tumor heterogeneity.

Currently, in the USA, the United Network for Organ Sharing (UNOS) has no formal policy regarding the use of LT for cHCC-CCA. Hence, patients with cHCC-CCA are not automatically eligible for MELD exception points unless a written appeal is approved by their respective regional review board. This is less of an issue currently as most patients with cHCC-CCA are misdiagnosed as HCC before LT and the correct diagnosis is typically established after LT. As diagnostic testing improves with increased recognition of cHCC-CCA as a unique disease entity, preoperative diagnosis of cHCC-CCA may increase. While awaiting high-quality data, LT should remain a potentially curative option in patients with unresectable cHCC-CCA with small tumor burden and acceptable tumor biology. It is expected that patients with cHCC-CCA will likely require more stringent criteria with regard to extent of tumor and tumor biology although the specific number of MELD exception points assigned by UNOS will need to be studied and discussed. For now, since cHCC-CCA appear to be biologically most similar to intrahepatic CCA, it may be reasonable to apply the same criteria as for LT for intrahepatic CCA, namely, a single nodule, less than 2–3 cm without poor histologic differentiation [28•]. Based on studies suggesting that CCA with higher serum CA 19-9 levels are associated with worse clinical outcomes, future studies should also explore whether a certain level of the CA 19-9 biomarker should be considered an exclusion criterion from LT.

Other Treatment: Local Ablation, Locoregional Treatment, Systemic Treatment

Local ablation and locoregional treatment are the most commonly used treatment modalities for HCC [29, 30]. However, there is little known about the efficacy of local ablation or locoregional treatment for the management of cHCC-CCA. In the absence of high-quality data, it would be reasonable to extrapolate efficacy data from the experience with HCC. Patients with small tumors who are not candidates for surgery or LT due to medical comorbidities may be eligible for local ablation. For patients with liver-limited multifocal tumors that are not amenable for local ablation, transarterial chemoembolization (TACE), transarterial radioembolization (TARE), or external beam radiation therapy are reasonable alternative options, depending on the number and location of the tumor nodules. In a single-center retrospective study of 50 patients in Korea that reported outcomes of patients who received TACE for histologically proven unresectable cHCC-CCA, 70% were classified as responders, achieving either a partial response or stable disease with successful (> 50%) tumor necrosis after TACE [31]. As expected, tumor response was related to tumor vascularity; 85% of hypervascular tumors vs. only 10% of hypovascular tumors responded to TACE ($p < 0.001$), suggesting that patients with a dominant hypervascular phenotype typical of HCC responded better to TACE. The median patient survival was 12.3 months. Tumor size (hazard ratio [HR], 2.49; $p = 0.028$), tumor hypovascularity (HR, 4.19; $p = 0.001$), Child-Pugh class (HR, 4.3; $p = 0.001$), and portal vein invasion (HR, 6.45; $p < 0.001$) were independently associated with worse overall survival. A small case series reported the efficacy of TARE in 10 patients with histologically proven unresectable cHCC-CCA who underwent 14 TARE treatments [32]. TARE was well tolerated, and the median overall survival was 10.2 months, with a best radiological response of 60% partial response and 40% stable disease by modified RECIST criteria.

Systemic treatment of cHCC-CCA is purely empirical and there are no data to support the use of one agent over another. Clinicians often determine the dominant phenotype of tumor based on radiologic characteristics or blood tumor marker tests (AFP vs CA 19-9) and recommend the standard of care treatment for either HCC or CCA. Most reported studies are case series that suffer from small sample sizes [33–35]. A recent French multicenter retrospective study of 30 patients with unresectable cHCC-CCA showed that treatment with gemcitabine plus cisplatin or oxaliplatin as first-line systemic therapy achieved 29% partial response, 5% stable disease, and 21% disease progression at first evaluation, with a median progression free survival of 9 months and overall survival of 16.2 months [33]. Underlying liver dysfunction signified by high serum bilirubin or positive viral hepatitis serology was associated with poor overall survival. Of note, only three quarters of cases in this study were confirmed by histology. The remaining cases were classified based on typical HCC or CCA histology with discordant CT-scan enhancement findings and serum tumor marker elevations (e.g., typical CCA histology with HCC enhancement pattern and elevated AFP or typical HCC histology with ICC enhancement pattern and elevated

CA19-9), which raises concerns about the possibility of misclassification. This study, one of the largest in the literature, included patients who received chemotherapy at seven different medical centers over a 10-year time period, highlighting the challenges of conducting studies on this relatively rarely diagnosed tumor type.

In the absence of a standard, evidence-based systemic treatment, molecular profiling of the tumor should be strongly considered in patients with advanced stage cHCC-CCA in order to identify potentially targetable genetic aberrations. A case was reported of a patient who was found to have a single nucleotide variant in the EGFR gene locus R521 [36]. The patient achieved a complete response on imaging after treatment with the combination of an EGFR inhibitor and a VEGF inhibitor. A recent phase 1/2, open-label, non-comparative, dose escalation, and expansion trial (CheckMate 040) showed that nivolumab is highly efficacious for the management of advanced stage HCC with an objective response rate between 15 and 20% [37]. Although the data are not as robust as HCC, several recent studies have shown promising efficacy of immunotherapy in CCA [38, 39]. There are number of clinical trials underway evaluating the efficacy and safety of immunotherapy in both HCC and CCA [40, 41]. With its phenotypic complexity and diversity, cHCC-CCA may carry a heavy mutational burden and may potentially be responsive to immunotherapy as has been shown for HCC and CCA. Currently, there are no reports that describe the efficacy of immunotherapy for the treatment of cHCC-CCA. This should be further investigated in future studies.

Conclusions

cHCC-CCA is an under-recognized primary liver cancer with histologic features of both HCC and CCA. With increasing depth of knowledge and better recognition of this diagnosis among clinicians, it is being diagnosed more frequently. cHCC-CCA appears to have a unique biology that is different from that of usual HCC or CCA. Determining the optimal strategies for diagnosis and treatment of this tumor are major unmet needs for clinicians and research scientists interested in this disease. Better understanding of the radiologic characteristics of cHCC-CCA tumors will be crucial to enhance suspicion of the diagnosis and may help target specific areas for core needle biopsy to maximize the diagnostic yield while minimizing sampling error. Curative surgical treatment should be considered whenever possible in patients with early stage disease with preserved liver function. Listing criteria for LT should be established. The roles of local ablation, locoregional treatment, and optimal systemic/targeted treatment are currently undefined and should be carefully assessed in future studies. Immunotherapy may be an effective strategy for management of cHCC-CCA and its safety and efficacy should be investigated. Currently, the relative difficulty of clearly establishing the diagnosis, performing integrated genetic and genomic characterization from tumor biopsies, and enrolling a sufficient number of patients into prospective clinical trials are major challenges and impediments to improving the care of this unique and relatively uncommon group of patients.

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Compliance with Ethical Standards

Conflict of Interest Lewis R. Roberts reports honorarium from an advisory board for Bayer, honorarium from an advisory board for Grail, speaker honorarium from Medscape, honorarium from consulting for ONCLIV and consulting for Axis. He also reports grants from Ariad, BTG, Gilead, Wako, and Redhill. Ju Dong Yang declares no potential conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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