Review Article

Combined intrahepatic cholangiocarcinoma and hepatocellular carcinoma

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Abstract: Hepatocellular carcinoma (HCC), the fifth most common cancer globally and third leading cause of cancer-related mortality is a heterogeneous disease with a highly variable clinical course. The inherent biological diversity of hepatic carcinomas may hinder therapeutic decision making and prognostication for patients. One distinct, albeit rare, subtype of primary hepatic carcinoma is combined intrahepatic cholangiocarcinoma and hepatocellular carcinoma (cHCC-ICC), which carries an overall worse prognosis than either HCC or intrahepatic cholangiocarcinoma (ICC) alone. cHCC-ICC is a primary hepatic neoplasm containing unequivocal elements of both HCC and ICC. This review will focus on understanding further the histopathology of this unique tumor type, current treatment approaches and prognoses for this rare patient population.

Keywords: Combined intrahepatic cholangiocarcinoma and hepatocellular carcinoma (cHCC-ICC); needle biopsy; surgical resection; prognosis

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Introduction

The majority of primary hepatic malignancies may be classified as either hepatocellular carcinoma (HCC), or intrahepatic cholangiocarcinoma (ICC), each with distinct clinicopathological features. Combined intrahepatic cholangiocarcinoma and hepatocellular carcinoma (cHCC-ICC) is so-called due to histologic evidence of both hepatocellular and biliary epithelial differentiation (1). It is a rare subtype of primary liver cancer, accounting for 1% to 14.2% of cases (1-5). The true incidence may in fact be higher, owing to frequent difficulty in accurate pathological assessment and the advanced nature of many of these tumors on presentation, precluding biopsy. This unique entity was first described by Allen and Lisa in 1949 and has been defined as the intimate intermingling of both a HCC component and CC component (2). Two histopathological classification schemes have been developed (2,6) (*Table 1*). Molecular analysis in one small case series demonstrated that cHCC-ICC is genetically closer to CC than HCC (7). Due to its rarity, much of the literature to date has been limited to small case series and isolated case reports. Consequently, there is a lack of understanding of the clinicopathological characteristics, prognoses and optimal management of patients with cHCC-ICC.

Epidemiology and risk factors

In terms of HCC as a disease entity, there is clear evidence of geographical variation in incidence which is reflective of variability of risk factors in different populations.

Underlying liver cirrhosis is present in 80% of patients with HCC. Common etiologic factors of hepatic cirrhosis include hepatitis C virus (HCV), hepatitis B virus (HBV),

Table 1 Pathological classification of cHCC-ICC

Allen and Lisa	Goodman
Type A	Type I
Double tumor (HCC and CC exist at different sites within the same liver)	Collision tumor (coincidental occurrence of HCC and CC within the same liver)
Type B	Type II
Combined type (HCC and CC exist at adjacent sites and mine with continued growth)	Transitional tumor (there is a transition from elements of HCC to elements typical of CC)
Type C	Type III
Mixed type (HCC and CC components are combined within the same mass)	Fibrolamellar tumor (resembles the fibrolamellar subtype of HCC but contains mucin-producing pseudoglands)

HCC, hepatocellular carcinoma; cHCC-ICC, combined intrahepatic cholangiocarcinoma and hepatocellular carcinoma.

alcohol misuse and non-alcoholic steatohepatitis (8-11). HBV infection is highly prevalent in Africa and Asia (11). HCV is the major risk factor for the development of HCC in Japan, Europe and North America (12). Alcohol misuse and non-alcoholic steatohepatitis, related to obesity and diabetes mellitus, are more commonly implicated in Western populations.

It is likely that such differences also exist for patients with cHCC-ICC, with varying prevalence of underlying hepatic cirrhosis between Eastern and Western populations. Most published series exploring cHCC-ICC originate from Asia and in these, the likelihood of viral hepatitis or liver cirrhosis in patients with cHCC-CC was intermediate between the high proportion seen in patients with HCC and the lower prevalence in patients with CC (3,5,13). In Asia, patients with cHCC-ICC are predominantly male. The prevalence for positive HBV and HCV serologies range from 17–58% and 0–75%, respectively. Underlying liver cirrhosis is present in 23.1–77.8% of cases (14). Taguchi *et al.* (5) reported that approximately 40% of cHCC-ICC patients in Japan presented with associated cirrhosis and a positive hepatitis serology.

In some studies, cHCC-CC seemed to be a variant of conventional HCC with cholangiocellular features and no significant differences regarding etiological risk factors among patients with cHCC-ICC and HCC were found (13,15,16). In general, patients with cHCC-ICC showed similar clinical and pathological features to HCC patients, including a mean age of onset in the sixth decade, male predominance, a high incidence of HBV infection, underlying chronic liver disease and elevated serum a-fetoprotein (AFP) levels (17).

In contrast, a study by Jarnagin *et al.* (1) reviewing a cohort of cHCC-ICC from the Western population reported a low prevalence of 15% of positive serology for either HBV or HCV, and complete absence of underlying chronic liver disease, resembling that in the ICC group.

However, given the rising incidence of HCV- and HBV-related HCC in the west, it is conceivable that the proportion of HCV- and HBV-related cHCC-ICC may also increase.

Based on a study of more than 20,000 patients with primary hepatic tumors recorded within SEER (Surveillance, Epidemiology and End Results Program of the National Cancer Institute), cHCC-ICC had an overall incidence of 1.3%; the age and sex specific incidence and geographic variation mirrored those of HCC (18).

Because cHCC-ICC is a tumor in which both HCC and CC components coexist, both risk factors for HCC and oncogenic agents for CC may predispose to cHCC-ICC. Previous studies have included patients with cHCC-ICC with documented risk factors that predispose to CC (1). The exact cause of CC is unknown but there are several well-defined risk factors, the most common of which is primary sclerosing cholangitis (PSC). The true incidence of CC in the setting of PSC is reported as 8–40% (19). Other abnormalities of biliary anatomy that are etiological factors for CC include choledochal cysts and Caroli's disease, a congenital condition (20,21). Multiple toxic and environmental factors implicated in the pathogenesis of CC may also predispose to cHCC-ICC including dioxin exposure, liver flukes, Thorotrast dye and dietary nitrosamines (22).

Table 2 Correlation between histopathological and CT findings

HCC pattern component	CC pattern component
Histology	
Trabecular growth	Glandular formation
Bile production	Cuboidal cells
Eosinophilic cytoplasm	Round nuclei
Prominent nuclei	Mucin production
or hyaline bodies	Abundant fibrous stroma
CT	
High attenuation on early phase	Low attenuation on early phase
Low attenuation on late phase	Low, iso-, or high attenuation on delayed phase

HCC, hepatocellular carcinoma; CT, computed tomography.

Clinical presentation and diagnosis

Typically cHCC-ICC is clinically silent, as is the case with both HCC and CC, until it presents with advanced disease. Common symptoms include painless obstructive jaundice, fatigue, abdominal discomfort, weight loss, pruritus, ascites, acute cholangitis, fever, hepatomegaly and a palpable gallbladder.

Due to striking similarities in the clinical features of cHCC-ICC to those of both conventional HCC and CC, preoperative diagnosis of cHCC-ICC with standard imaging is virtually impossible.

The vast majority of studied patients were initially misdiagnosed either as HCC or CC despite extensive staging scans (23). The accurate preoperative diagnosis of cHCC-ICC does have important implications in terms of management decisions and prognosis, as the treatment selected may differ from that for HCC or CC, depending on the predominant component of the tumor and any underlying cirrhosis. In particular, the frequency of lymph node metastases in cHCC-ICC may be as high as that in CC, underscoring the need for systemic nodal dissection as part of curative surgery (4).

Serologic tumor markers are also of limited benefit for preoperative diagnosis of cHCC-ICC because high levels of serum AFP and low levels of carcinoembryonic antigen (CEA) and/or carbohydrate antigen 19-9 (CA19-9) are most commonly detected (24). Also, previous research has shown that there is no significant difference in AFP levels between the cHCC-ICC group and the HCC group, although a simultaneous increase in serum CA19-9 and AFP plus a liver mass on imaging studies may suggest cHCC-CC (25).

When selecting patients for appropriate treatments, radiologic studies assist in detecting the presence of underlying cirrhosis, extensive intra-hepatic disease, vascular involvement, and extra-hepatic metastases.

There is no characteristic description per se of cHCC-CC on the different imaging modalities. On ultrasound cHCC-ICC usually appears as a hypoechoic mass with a hyperechoic component (26). Computed tomography (CT), positron emission tomography (PET), and fusion PET CT have all been employed to diagnose cHCC-ICC, with varying results. As the histological type of hepatic tumor influences its enhancement characteristics on dynamic CT, findings for cHCC-ICC differ based on the histological proportion of the HCC and CC components and the volume of fibrous stroma (24,27-29) (*Table 2*).

Dynamic imaging techniques [CT, magnetic resonance imaging (MRI)] exploit the characteristic vascular profile of HCC, which is almost exclusively arterial. cHCC-ICC lesions resembling HCC are identified by intense contrast uptake during the arterial/early phase, whereas there is washout of contrast during the delayed/venous phase (30-33). Contrary to this, in the case of cHCC-ICC lesions resembling CC there is evidence of low attenuation in the early phase, and low, iso- or high attenuation in the delayed phase (31-33). Moreover, in one study it was observed that, in the CC type of cHCC-ICC, CT findings mirrored those of CC but virus markers and serum AFP levels were almost equivalent to those found in patients with a HCC type of cHCC-ICC (29). Thus, cHCC-ICC with a CC pattern component can, in select patients, be diagnosed using the combination of CT findings, serum AFP levels and serum virus markers.

PET can reliably detect CC as small as 1 cm (34), but its detection rate for cHCC-ICC is only about 57% (35). However, fusion PET CT has demonstrated utility in identifying extrahepatic metastases in both HCC and cHCC-ICC patients, with detection rates as high as 98% (35).

Definitive diagnosis of cHCC-ICC on the basis of cytological material alone is difficult, if not impossible, because of a lack of uniform agreement on the cytological criteria for cHCC-ICC. A needle core biopsy is the preferred method for tissue sampling, as it allows the pathologist not only to diagnose malignancy but also to evaluate the architecture/pattern of the tumor, which is critical for accurate diagnosis of cHCC-ICC. Needle

core biopsies are not without their limitations however, as given the diverse appearance of these tumors and inherent heterogeneity, the material biopsied may contain only one of the two components resulting in a misdiagnosis of either HCC or CC. The diagnostic yield of biopsy for pre-operative diagnosis of cHCC-ICC is low as reported by Taguchi *et al.* (5); none of the 23 patients with cHCC-ICC showed features of cHCC-ICC on preoperative liver biopsies, 20 out of 23 had HCC on biopsy and the other three were diagnosed with CC on biopsy. Final diagnosis of this entity is usually made on surgical specimens or liver explant.

Identification and classification

Classification of cHC-ICC has been an evolving field over several decades. The first true detailed characterization of cHCC-ICC as an individual entity was in 1949 by Allen and Lisa who reported that the combined tumor accounted for approximately 1.4% of all primary hepatic malignancies (2). In 1989, The Liver Cancer Study Group of Japan formulated its own classification of cHCC-CC (4). According to this system, cHCC-CC was again classified into three types: double cancer, combined type, and mixed type. In 1985, Goodman *et al.*, while reporting 24 cases of cHCC-ICC, suggested a third new system of classification: collision, transitional and fibrolamellar tumors (6).

According to the World Health Organization (WHO), cHCC-ICC is defined as a tumor with an intimate and unequivocal admixture of both HCC and ICC cells (36). This category should not be used for tumors in which either form of growth is insufficiently differentiated for positive identification. The WHO defines the hepatocellular component of cHCC-ICC by the presence of bile production, bile canaliculi and a trabecular pattern of growth. The glandular component is defined by the presence of true gland formation with mucin production. Current WHO guidelines classify cHCC-ICC into two subtypes: cHCC-ICC classical type and cHCC-ICC with stem cell features. The latter type is extremely rare and is further subcategorized into the following three subtypes: typical, intermediate cell and cholangiocellular subtype. The most common form of cHCC-ICC is the classical type. It contains areas of typical appearing HCC intermixed with CC and identifiable transition zones, where the two components merge and show tumor cells with intermediate morphology.

The variation in the reported incidence of cHCC-ICC has been attributed in part to lack of uniform criterion for diagnosis and classification of these tumors. Some reports include only cHCC-ICC of Allen type C (1,15) whereas, others incorporate all three types of cHCC-ICC (5,16,37).

The diagnosis of cHCC-ICC is reliant on unequivocal evidence of both hepatocellular and biliary epithelial features within the same tumor. Features suggestive of HCC differentiation include trabecular or pseudoglandular growth pattern, bile in the canaliculi, and carcinoma cells with intracellular inclusions such as fat, Mallory bodies and alpha-1 antitrypsin typically found in hepatocytes. Features resembling CC include a desmoplastic stroma, and carcinoma cells forming glandular structures and less commonly, producing mucin. A solid diagnosis of cHCC-ICC mandates an interface where HCC and CC components intimately intermingle with each other (24). Classical histological features of cHCC-ICC are shown in *Figure 1*. Notably, however, some tumors may show varying degrees of hepatocellular and cholangiocytic differentiation without a definable interface, and tumor classification can thus be challenging.

Immunohistochemistry plays a key role in confirming the individual components of the tumor as well as demonstrating transition zones. Confirmation of a HCC element is provided by immunohistochemical staining with hepatocellular markers [including hepatocyte paraffin 1 (HepPar-1) monoclonal antibody and Arginase 1], canalicular staining with polyclonal CEA or CD10 and demonstration of sinusoidal "capillarization" by CD34. The CC component is diagnosed by positive immunohistochemical staining for CK7, CK19 and MOC31, and luminal reactivity to epithelial membrane antigent (EMA) (38-40). A mucin stain [periodic acid-Schiff stain after diastase digestion (dPAS) or mucicarmine] may also aid in demonstrating the CC component by highlighting intracytoplasmic mucin (36). Transition zones have been shown to stain for both typical biliary cytokeratins CK7 and CK19, as well as the hepatocellular markers HepPar-1 and Arginase 1. Recently, branched chain *in situ* hybridization for albumin has been shown to be an additional tool sensitive in detecting epithelial tumors of hepatic origin including both HCC and CC (41).

The cell of origin in cHCC-ICC remains unknown. Studies have shown that HCC, CC and many other tumors may originate from stem cells (42-44). It is generally accepted that adult hepatic stem cells are the hepatic oval cells and they are capable of biliary or hepatocytic differentiation (43,44).

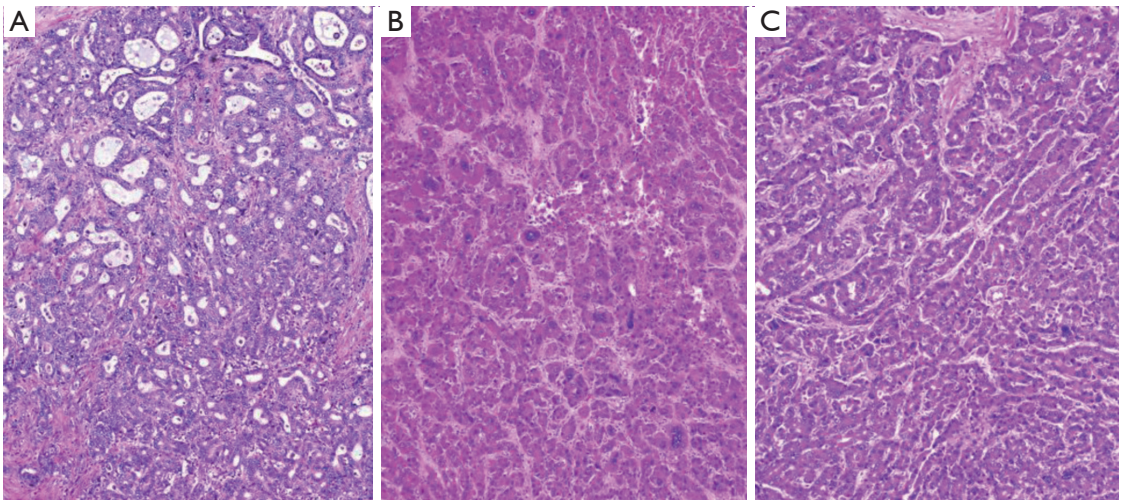

Figure 1 Classical histological features. Photomicrograph of a combined cholangiocarcinoma-hepatocellular carcinoma (magnification, ×100). This tumor shows two distinct components that are characteristic of cholangiocarcinoma (A) and hepatocellular carcinoma (B) respectively. Interestingly, there are also regions where the tumor shows mixed features with glandular architecture and hepatocellular cytology (C).

In cases of cHCC-ICC, it has been observed that the tumor is derived from a single clone, and the histological diversity is a phenotypic expression of divergent differentiation (45). Yano *et al.* (46) established a primary cell line derived from resected cHCC-ICC and showed that it differentiated to not only the characteristics of HCC but also those of CC under different growth conditions, suggesting that cHCC-ICC arise from stem cells. Woo *et al.* (47) investigating the comparative gene expression profile of ICC, HCC and cHCC-ICC tumors observed that ICC and HCC could be clearly distinguished from one another by their gene expression profile. Further, 5/7 (71.4%) cHCC-ICC tumors clustered together with the ICC group, suggesting that cHCC-ICC is closer to ICC (than HCC) at the molecular level.

Treatment approaches

There are no clear guidelines with regard to the management of cHCC-ICC. However, surgical resection is the only treatment offering the possibility of a cure. Factors which influence eligibility for surgery include underlying cirrhosis, the patient's general medical condition, tumor extent and local anatomic conditions. The main goal should be complete surgical excision with negative margins and limited impingement on liver function. Severe liver dysfunction predicts a dismal prognosis, irrespective of the technical success of the procedure.

cHCC-ICC tends to behave like HCC with respect to portal and hepatic venous infiltration, and like CC with regard to lymph node metastasis (6,48). At autopsy, lymph node metastasis was observed in 76% of patients with cHCC-ICC (4). Compared with this, lymph node metastasis was present in only 30% of HCC patients and 69% of CC patients (4). Consequently, hepatic resection with hilar lymph node dissection is the recommended treatment for cHCC-ICC in non-cirrhotic patients. Resectability in this group has been reported to be as high as 78% (1). However, the prognostic benefit of lymphadenectomy for cHCC-CC remains controversial (49-52). Whether the addition of systemic chemotherapy in a neoadjuvant or adjuvant setting in patients undergoing node dissection improves prognosis also remains an open question.

For cirrhotic patients, hepatic resection has the potential for debilitating complications (11), so the adoption of strict selection criteria is imperative to negate significant peri-operative as well as overall morbidity and mortality. The reduced functional reserve of cirrhotic patients limits the extent of surgery.

The role of liver transplantation in the management of HCC is well accepted and defined. Liver transplantation is an effective option for patients with HCC and cirrhosis corresponding to the Milan criteria (53), i.e., solitary tumors of <5 cm or up to three tumor nodules each of

which is smaller than 3 cm. Because of the high rate of tumor recurrence and a lack of positive prognostic variables, liver transplantation as a treatment for CC is generally considered to be contra-indicated (54,55).

Data about the role of liver transplantation in the management of cHCC-ICC are lacking. In a study of three cHCC-ICC patients treated by liver transplantation, two patients survived at 25 and 35 months after liver transplantation respectively (56). In this study, the survival of these patients surpassed that of patients who underwent resection; however, the small size of the study makes any conclusions unreliable, and more research is required. Panjala *et al.* (57) recently reported that among patients who underwent liver transplant for HCC, 12 had mixed cHCC-ICC and ICC in the explant. The tumor recurrence rate was 58%, and the 5-year overall patient survival rate was 16% in cHCC-ICC patients who underwent liver transplantation. Sapisochin *et al.* (58) reported survival data on a similar 14 patients who were found to have cHCC-ICC on the explant. Eight of the 14 patients (57%) had tumor recurrence after a median follow-up of 32 months. The median disease-free survival time was 8 months. The cumulative risk of tumor recurrence was 40% and 70% at 1 and 5 years, respectively, for those 14 patients. There are no published reports describing non-surgical treatment options for cHCC-ICC.

Transarterial chemoembolisation (TACE) and percutaneous treatments such as percutaneous ethanol injection (PEI) and radiofrequency ablation (RFA) are the most widely used treatments for unresectable HCC and in the setting of post-resection recurrence (59,60). However, many cHCC-ICC tumors are less vascular and more fibrotic than HCC, and thus are less likely to respond to either TACE or PEI.

Other approaches, such as RFA or cryoablation, may be of benefit for treatment of recurrence in select patients (61). The pattern of local recurrence of cHCC-ICC is thought to reflect that of CC rather than HCC, indicating the dominant prognostic role of the CC element of cHCC-ICC (23,48). Therefore, patients who are unresectable due to locally advanced disease or local recurrence in the absence of distant metastases may be candidates for palliative radiation therapy with or without concomitant chemotherapy. Symptomatic and local tumor control have been reported with such a treatment paradigm (6,62,63).For those patients with widespread metastatic disease, systemic chemotherapy may be an option for fit patients; however, the reported response rates are low (64-66).

Survival

Survival is determined by disease stage at diagnosis and, perhaps, the absence of nodal involvement. Partial hepatectomy with hilar lymph node dissection can result in 5-year survival rates exceeding 50% in patients with early stage disease (23,50). Post-surgical resection, the reported median length of survival ranges from 20 to 47 months (1,3,15,24,39,67).

Vascular and lymph node invasion and the presence of satellite metastases, which are related to and associated with tumor size, have been suggested as significant predictors of poor prognosis after resection (3,15,23,33,68). In contrast, patients with unresectable tumors fared poorly, with no survivors reported beyond 2 years (1,39).

In a small retrospective study of 25 patients (17), multivariate analysis showed that elevated CA 19-9 (≥80 U/mL) and the presence of intrahepatic biliary dilatation were independent predictors of poor survival. In general, the survival rate of cHCC-ICC was either lower than that reported for HCC or CC (1,13-15,67) or intermediate between HCC and CC (3,17,23). Lower survival after surgical resection of cHCC-ICC is likely related to the lack of effective treatment options for disease recurrence, which is as high as 95% within the first 2 years (13,15,33).

Conclusions

cHCC-ICC is an uncommon primary liver neoplasm which is increasingly being recognized as a distinct entity. Its true incidence may be higher than that reported due to historical diagnostic difficulties in distinguishing between patients with ICC, HCC and those with cHCC-ICC. The clinical behavior and prognosis of cHCC-CC has overlapping features between that of HCC and ICC. Pre-operative diagnosis of cHCC-CC is crucial but remains difficult. Successful preoperative diagnosis is dependent upon maintaining a high index of suspicion, appropriate selection of imaging studies, obtaining histology if possible, and correlating the results with serum AFP and CA 19-9. As cHCC-ICC is a rare disease entity, no clear treatment paradigm has yet been defined. Currently, surgery remains the only effective treatment option. In those eligible for surgery, the recommended approach is partial hepatectomy with hilar lymph node dissection. The exact role of liver transplantation remains unclear and requires further investigation. These diagnostic and therapeutic dilemmas,

which in part relate to the origin of cHCC-ICC from two different tumor entities, combined with the inherent poor prognosis of cHCC-ICC highlight the need for increased effort in understanding the pathogenesis to improve diagnosis and ultimately treatment outcomes for patients with this malignancy.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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