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Review Article

Update on the Diagnosis and Treatment of Combined Hepatocellular Cholangiocarcinoma

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Abstract

Combined hepatocellular-cholangiocarcinoma (cHCC-CCA) is a unique type of liver tumor that contains both hepatocellular carcinoma and cholangiocarcinoma components within a single tumor. The fifth edition of the World Health Organization classification provides a definition and diagnostic criteria for cHCC-CCA. However, the heterogeneous histomorphology and presentation resulting from variation of the proportion of each component poses challenges for clinical diagnosis and treatment. A diagnosis of cHCC-CCA may be suggested by the synchronous elevation of serum tumor markers for hepatocellular carcinoma and cholangiocarcinoma, a mixed enhancement pattern on imaging, and a discrepancy between the elevation of tumor marker and the imaging enhancement pattern. Histopathological examination using hematoxylin and eosin staining is considered the gold standard for diagnosing cHCC-CCA, and comprehensive examination of resection or biopsy specimens is crucial for an accurate diagnosis. Currently, there is no standard treatment for cHCC-CCA, and surgery is the mainstay. Anatomic hepatectomy with lymphadenectomy is among the recommended surgical procedures. The role of liver transplantation in the management of cHCC-CCA is still uncertain. Transarterial chemoembolization may be effective for unresectable cHCC-CCA, particularly for hypervascular tumors. However, the available evidence does not support systemic therapy for advanced cHCC-CCA. The prognosis of cHCC-CCA is generally poor, and there is no established staging system. Further research is needed to better understand the histogenesis and clinical management of cHCC-CCA. This review provides an overview of the current literature on cHCC-CCA with a focus on its clinical characteristics, pathological diagnosis, and management.

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Introduction

Hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC) are two distinct types of liver cancers that differ in terms of their etiology, histology, molecular features, and clinical outcomes.[1,2] Combined hepatocellular-cholangiocarcinoma (cHCC-CCA) is a rare form of liver cancer that contains both HCC and ICC components within a single tumor. The varying proportions of these components contribute to the heterogeneous nature of cHCC-CCA, posing challenges for accurate diagnosis and treatment decisions.[3] Despite being first described in 1903, cHCC-CCA remains poorly understood up to now because of its rarity and complexity.[4] The lack of standardized terminology and diagnostic criteria led to diagnostic confusion and ambiguity in literature before the publication of the fifth edition of the World Health Organization (WHO) classification in 2019.[5] However the unique characteristics of cHCC-CCA have attracted global research interest and recent years have seen an increase in research on cHCC-CCA.[6] This review aims to provide an overview of the latest updates on cHCC-CCA, with a focus on its clinical and imaging characteristics, pathological diagnosis, and clinical management.

Clinical characteristics

cHCC-CCA, as a subtype of primary liver neoplasm, is less prevalent compared to HCC or ICC. From 2004 to 2014, the incidence of cHCC-CCA in the USA was 0.05 per 100,000 per year, but there has been a recent increase in both incidence and mortality rates.[7,8] Although cHCC-CCA accounts for 0.4–14.2% of primary liver neoplasms, its true incidence may have been underestimated in the past.[9,10] The lack of clear and consistent definition and diagnostic criteria for cHCC-CCA have resulted in inconsistent and nonreproducible findings

Keywords: Combined hepatocellular-cholangiocarcinoma; Clinical characteristics; Imaging characteristics; Pathological diagnosis; Treatment.

Abbreviations: AFP, alpha-fetoprotein; CA 19-9, carbohydrate antigen 19-9; CEUS, contrast-enhanced ultrasound; cHCC-CCA, combined hepatocellular-cholangiocarcinoma; HCC, hepatocellular carcinoma; HE, hematoxylin and eosin; ICC, intrahepatic cholangiocarcinoma; ICI, immune checkpoint inhibitor; LI-RADS, liver Imaging Reporting and Data System; LT, liver transplantation; RE, radioembolization; TACE, transarterial chemoembolization; WHO, World Health Organization.

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regarding its incidence and clinical features across different studies.[11] Risk factors associated with the development of cHCC-CCA, such as hepatitis B, hepatitis C, and cirrhosis, are similar to those of HCC in Asian populations.[12] However, studies conducted in Europe and the USA have reported that most cases of cHCC-CCA occur without accompanying chronic liver diseases and arise de novo.[13] These findings suggest that geographical factors may influence the clinical characteristics of patients with cHCC-CCA. Furthermore, one study has identified a frequent occurrence of cHCC-CCA in patients who underwent transarterial chemoembolization (TACE) for HCC, indicating a potential association that warrants further investigation.[14]

The clinical features of patients with cHCC-CCA are similar to those observed in patients with HCC or ICC. Symptoms of cHCC-CCA include right upper quadrant discomfort, abdominal pain, fatigue, fever, and weight loss etc.[15] Studies from Asian countries indicated a higher prevalence of cHCC-CCA in men, whereas studies in Western countries did not report any significant sex-related differences.[14] The median age of patients diagnosed with cHCC-CCA typically ranges from 50 to 75 years.[13] cHCC-CCA tends to have multiple tumor nodules, and intrahepatic metastases may consist of one or both types of the cHCC-CCA components. The biological behavior of cHCC-CCA is characterized by a high incidence of lymphatic metastasis, commonly observed in patients with ICC, as well as vascular invasion, commonly observed in patients with HCC. The rate of lymphatic metastasis in patients with cHCC-CCA ranges from 12% to 33% and the incidence of microvascular invasion may reach 68.7%.[15,16]

The positive rate of alpha-fetoprotein (AFP) (>20 ng/mL) in patients with cHCC-CCA is reported to be lower than that in patients with HCC but higher than that in patients with ICC (58.3%, 66.5%, and 13.7% respectively).[17] Similarly, the levels of carbohydrate antigen 19-9 (CA 19-9) in patients with cHCC-CCA are lower than those in ICC but higher than those in HCC.[7] The simultaneous increase of serum AFP/des-γ-carboxy prothrombin and CA 19-9 may support a diagnosis of cHCC-CCA. However, this simultaneous elevation of tumor markers is only observed in a small proportion of cHCC-CCA patients, and its sensitivity for diagnosing cHCC-CCA is only 17.8%.[18,19] Therefore, it is challenging to diagnose cHCC-CCA solely based on clinical presentations and laboratory findings.

Imaging characteristics

Preoperative imaging plays a crucial role in providing valuable information regarding the morphology and composition of tumors that exhibit overlapping features of HCC and ICC, known as cHCC-CCA.[7] The radiographic features of cHCC-CCA are primarily determined by the predominant components. Notably, cHCC-CCA often exhibits an indistinct margin (82.8%) and an irregular shape (60.9%) on gray ultrasound (US), resembling ICC rather than HCC.[20] Contrast-enhanced ultrasound (CEUS) enables real-time visualization of tumor echogenicity and microcirculation. The echogenicity and enhancement pattern of cHCC-CCA may be influenced by the proportion of each component within the tumor, which contributes to the heterogeneity observed.[21] This heterogeneity can aid in the diagnosis of cHCC-CCA. However, it is worth noting that the Liver Imaging Reporting and Data System (LI-RADS) categories are associated with misdiagnosis in approximately half of all cHCC-CCA lesions.[22] To improve diagnostic accuracy, a combination of tumor markers and CEUS findings has been found to have a moderate accuracy rate ranging from 73.3% to 76.9% in the diagnosis of cHCC-CCA.[23]

The imaging characteristics of cHCC-CCA observed with computed tomography (CT) and magnetic resonance imaging (MRI) have significant overlap with those of HCC and ICC. These characteristics include capsular retraction, biliary dilatation, pseudocapsule, enhancement pattern, and abnormal perfusion.[24] The radiological appearance of cHCC-CCA is largely determined by the predominant component. For instance, cHCC-CCA with a predominant HCC component may display an wash in and wash out pattern, while lesions with a predominant ICC component may have progressive centripetal enhancement or persistent enhancement.[25] LI-RADS indicates that a targetoid appearance is commonly observed in cHCC-CCA cases, with peripheral early enhancement and late washout, and central persistent enhancement.[22] A mixed enhancement pattern, characterized by both washout and persistent enhancement within a liver nodule, has a sensitivity of 48% and a specificity of 81% for diagnosing cHCC-CCA.[25] (Figs. 1 and 2) However, it is important to note that the imaging appearance of cHCC-CCA is highly heterogeneous, making radiological diagnosis challenging.

In general, elevated levels of AFP are typically associated with HCC and elevated levels of CA 19-9 are associated with ICC. However, in cases where a tumor exhibits imaging characteristics of HCC along with elevated CA 19-9 levels, or imaging characteristics of ICC along with elevated AFP levels, cHCC-CCA may be suspected. In such cases, it is recommended to perform a biopsy for pathological confirmation.[26] Li *et al*.[18] found that a significant proportion of cHCC-CCA patients exhibited a discrepancy between tumor marker elevation and imaging appearance on CEUS or contrast-enhanced CT (51.1% and 53.5% respectively). Zhou *et al*.[27] proposed new diagnostic criteria for cHCC-CCA by combining LI-RADS with serum biomarkers. The proposed criteria stated that one or more of the following conditions should be met: (1) arterial phase hyperenhancement (APHE) on CEUS and CT/MRI LR-M; (2) CEUS LR-5 and CT/MRI LR-5 with elevated CA19-9; and (3) CEUS LR-M and CT/MRI LR-M with elevated AFP.

Pathological diagnosis

Histopathological examination using hematoxylin and eosin (HE) staining is the gold standard diagnosis of liver tumors, including cHCC-CCA. However, the concept and definition of cHCC-CCA have undergone changes over the past years, leading to confusion in the literature. In 2018, an international group of pathologists, radiologists, and clinicians proposed a consensus for cHCC-CCA terminology and recommended the diagnosis of cHCC-CCA be based solely on histopathology with HE staining.[28] These recommendations were subsequently incorporated into the fifth edition of the WHO classification of digestive tumors, where cHCC-CCA was clearly defined as a primary liver carcinoma with the unequivocal presence of both hepatocytic and cholangiocytic differentiation within the same tumor regardless of the percentage of each component.[5] The ICC component in cHCC-CCA usually presents histologically as the small-duct type of ICC which shows a variable but usually small tubular or acinar adenocarcinoma exhibiting nodular growth and invading the parenchyma.[29] (Figs. 3 and 4) Previously recognized as subtypes of cHCC-CCA, such as double cancer (Allen and Lisa type A), collision tumor (Goodman type I), fibrolamellar HCC (Goodman type III), HCC morphology with the immunophenotype of cholangiocytic markers or stem cell markers, ICC with immunophenotypes of hepatocytic markers or stem cell markers, and ICC with in situ hybridization markers for hepatocytic differentiation, are no longer considered as cHCC-CCA

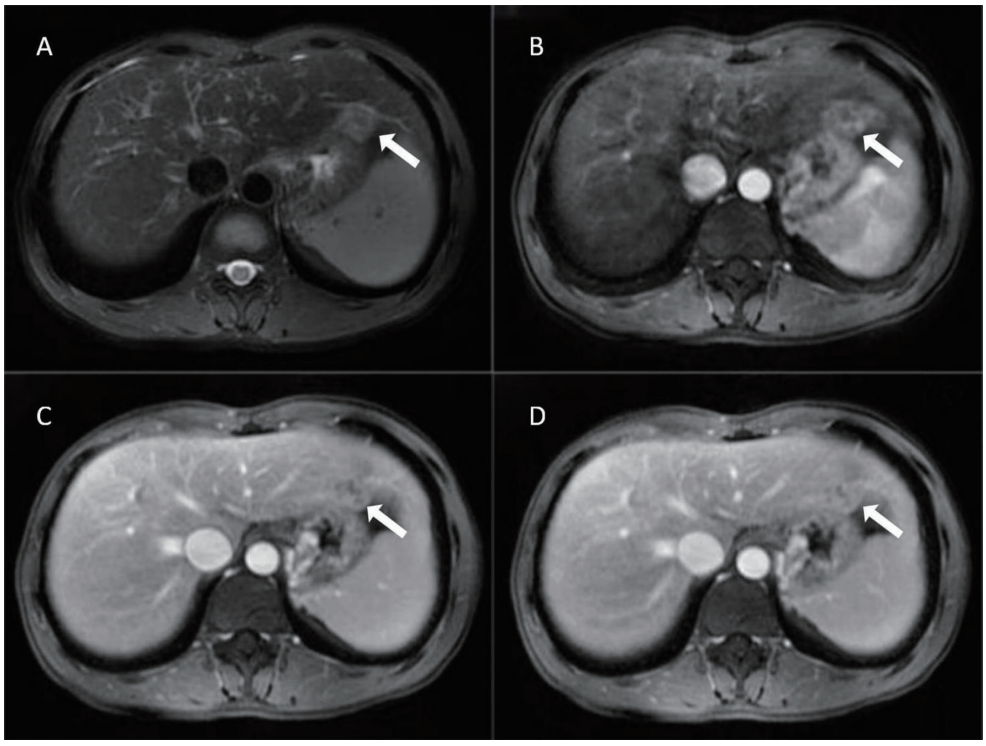

Fig. 1. A cHCC-CCA lesion as shown on MRI. (A) An irregular hyperintensity tumor on T2-weighted imaging. During contrast study, the lesion shows heterogenous enhancement in the arterial phase (B), and mixed washout and persistent enhancement in the portal phase (C) and delayed phase (D). cHCC-CCA, combined hepatocellular cholangiocarcinoma; MRI, magnetic resonance imaging.

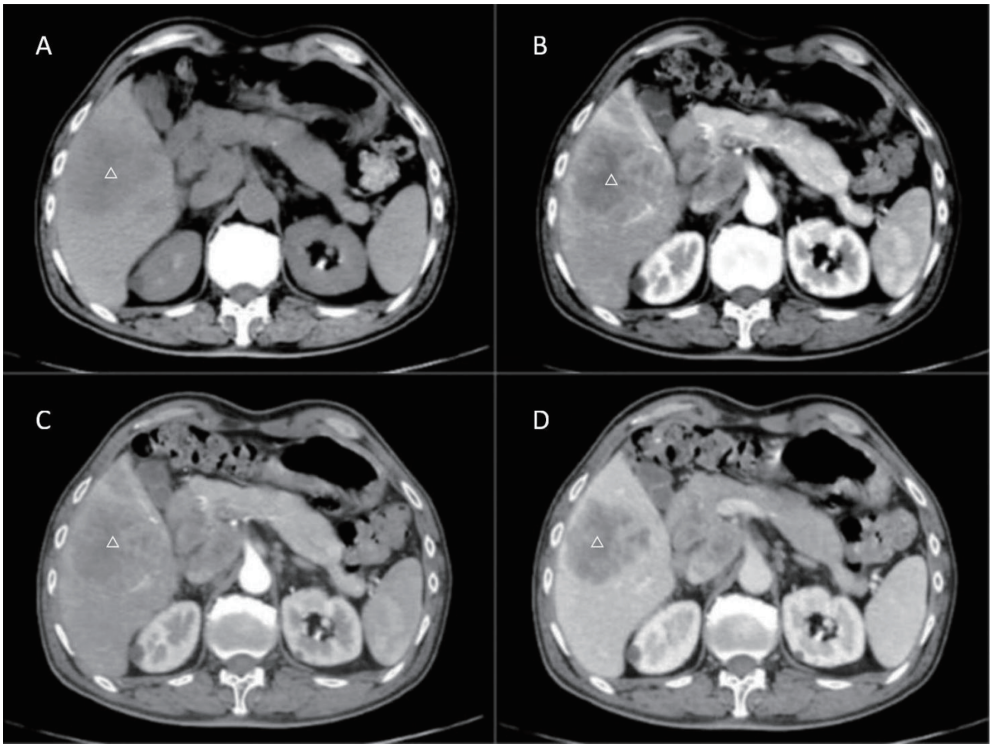

Fig. 2. Figure 2. A cHCC-CCA lesion as shown on CT. A low-density lesion on non-contrast images (A) and a heterogenous enhancement pattern in the nodule in the arterial phase (B). The enhancement of the lesion is persistent on the portal (C) and delayed phase (D). cHCC-CCA, combined hepatocellular cholangiocarcinoma; CT, computed tomography.

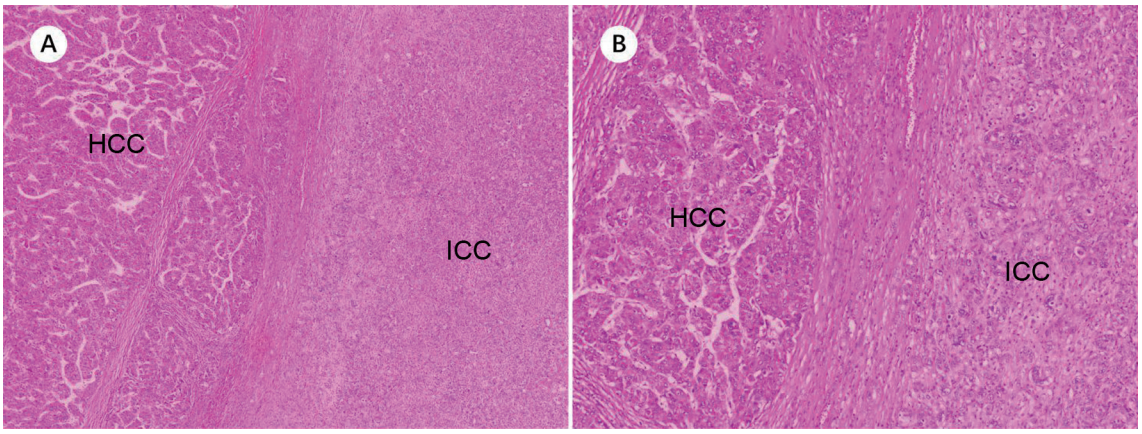

Fig. 3. Combined hepatocellular cholangiocarcinoma without transition zone. (A) The HCC component shows a trabecular pattern, and the ICC component shows a tubular pattern (HE staining, 40×). (B) There is no transition zone between the HCC and ICC components (HE staining, 100×). HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocellular carcinoma; HE, hematoxylin and eosin.

according to the fifth edition of WHO classification.[30] It is worth noting that prominent pseudoglands commonly found in conventional HCC tend to be mistakenly identified as true glandular structures and the reactive ductular reaction at the edge of HCC tends to be considered as an ICC component, leading to the misdiagnosis of cHCC-CCA.[12] Some variants of ICC and ICC arising adjacent to hepatocellular nodular lesions (nodular regenerative hyperplasia) may have histopathological features that resemble cHCC-CCA. However, regardless of the differentiation and immunophenotype, ICC lacking a distinct HCC component should not be diagnosed as cHCC-CCA.[31]

A thorough examination of the resection specimen is essential in accurately diagnosing cHCC-CCA in surgical patients. Currently there are no definitive guidelines for the pathological assessment of resection specimens. It is recommended to section the specimen in a sequential mothed, with thin intervals (e.g., 0.5 cm) and examine all cut surfaces carefully for tumor nodules. Special attention should be given to areas that appear different and to the transition between these areas, which should be sampled meticulously.[32] In large tumors, it is strongly recommended to extensively sample the specimen with at least one block/cm during macroscopic analysis, to avoid missing the small percentage of neoplastic components.[33] The initial and most crucial step in the diagnostic procedure is a thorough histological evaluation of HE-stained sections at low-power magnification.[12] Currently, there is no requirement for quantifying the percentage of each component. Immunohistochemistry is supportive but not essential for the diagnosis of cHCC-CCA.[31]

Fine needle aspiration biopsy may not be adequate for sampling the cHCC-CCA tumor, potentially resulting in a misdiagnosis as HCC or ICC. In practical terms, a biopsy often only captures a small portion of a highly heterogenous tumor, making it difficult to accurately diagnose a suspected cHCC-CCA. One study proposed that in cases where imaging features are heterogeneous or overlapping, an extended tissue biopsy should be performed on different areas of the tumor to aid in the diagnosis of cHCC-CCA.[34] Krishna *et al*.[35] recommended obtaining multiple core biopsies from different areas of a tumor to ensure sufficient sampling for an accurate diagnosis. Given the high intratumoral heterogeneity, further research is needed to determine the optimal histologic sampling method for diagnosing cHCC-CCA through biopsy.

Histogenesis of cHCC-CCA

Owing to its unique histological characteristics, the cellular

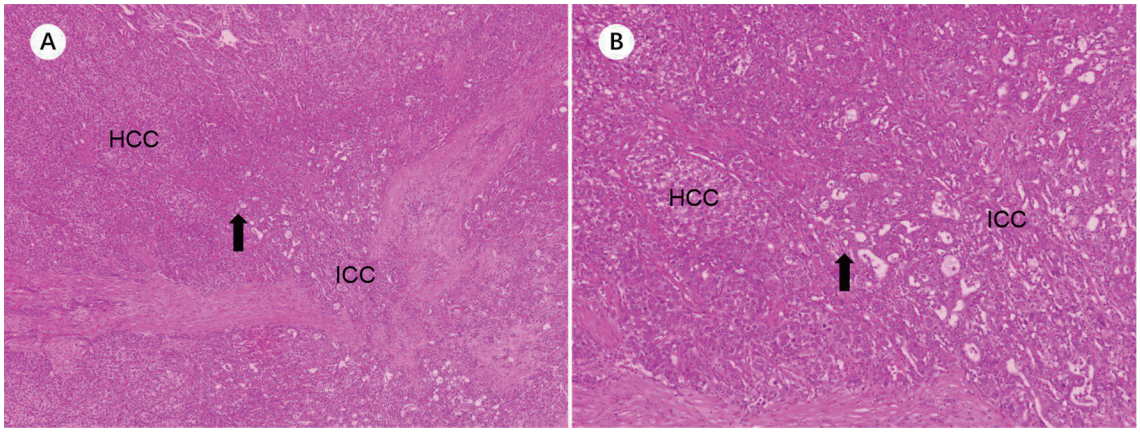

Fig. 4. Combined hepatocellular-cholangiocarcinoma with a transition zone. (A) The tumor shows both a hepatocytic differentiation area of the trabecular pattern and a cholangiocytic differentiation area of the tubular pattern (HE staining, 40×). (B) There is a transition zone between the HCC and ICC components (arrow; HE staining, 100×). HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocellular carcinoma; HE, hematoxylin and eosin.

Table 1. Prognosis of cHCC-CCA after liver resection or liver transplantation

Author	Population	Cases	Publication year	Liver resection				Liver transplantation		
				1-year OS	2-year OS	3-year OS	5-year OS	1-year OS	3-year OS	5-year OS
Peng S[48]	USA	183	2023	76.1		44.5	42.7	86.3	73.3	61.4
Teufel A[49]	German	129	2023	50	36					
Zhang G[50]	China	95	2022	73.9		38.2	23.6			
Wu Y[51]	China	127*	2023	67.3	51.2	39.7				
		81#		80.2	66.5	57.3				
Tang Y[52]	China		2021	63.9			39.5			
Kim M[53]	South Korea	153	2021	92.1		70.9	61.7			
Zhou Q[47]	China	206	2021	78		56	44			
Wakizaka K[16]	Japan	28	2019	57.9		33.4	25.1			
Dageforde LA[45]	USA	67	2021					89.1	77.1	70.1
Jaradat D[46]	German, Turkey, Jordan	19	2021					57.1	38.1	

*Microvascular invasion positive; #Microvascular invasion negative. cHCC-CCA, Combined hepatocellular-cholangiocarcinoma; OS, Overall survival.

origin and histogenesis of cHCC-CCA have attracted great interest but remain unclear. Two prevailing hypotheses suggest that cHCC-CCA may arise from either a malignant transformation of hepatic progenitor cells or transdifferentiation of HCC or ICC cells.[36,37] Recent molecular evidence has provided support for the notion that cHCC-CCA may have a common clonal origin, likely originating from hepatic progenitor cells (HPC) capable of differentiating into both hepatocytes and cholangiocytes.[38,39] This is further supported by the successful development of cHCC-CCA in mice through the inoculation of cells from a cHCC-CCA cell line that expressed the HPC marker EpCAM.[40] However, transduced mouse hepatoblasts, adult hepatocytes, and progenitor cells with driver oncogenes were shown to acquire progenitor markers and give rise to cHCC-CCA in mice.[41] The cellular origin and histogenesis of cHCC-CCA are being investigated and there is still ongoing debate regarding its cellular origin.[42]

A recent molecular study showed that HCC and ICC components within cHCC-CCA tumors usually have shared key genetic events and clonal patterns.[43] Various sequencing studies, including whole-exome, RNA, and single-nucleus sequencing, have revealed that cHCC-CCA frequently harbors mutations in *TP53* (49%), *TERT* promoter (23%), *AXIN1* (10%), and *KMT2D* (9%).[38] These mutations are also commonly found in HCC and ICC. However, whether cHCC-CCA more closely resembles HCC or ICC in terms of its genetic profile remains a controversial issue. Additionally, these findings have not yet identified straightforward molecular biomarkers to aid in the clinical diagnosis of cHCC-CCA.

Treatment and prognosis

The treatment for cHCC-CCA has not yet been standardized. Surgical resection is considered the preferred treatment option, with liver transplantation having favorable outcomes for early-stage cHCC-CCA.[44] Anatomic hepatectomy with lymph node dissection is recommended due to the characteristics of the two components of cHCC-CCA, namely HCC spreading through portal veins and ICC developing lymph node metastases.[7] However, the benefit of lymphadenectomy for long-term survival is still a matter of debate. The prognosis of patients who undergo resection for cHCC-CCA has been reported to vary across different studies, as shown in Table 1.[16,45–53] Prognostic factors after cHCC-CCA resection include tumor diameter >5 cm, intrahepatic metastases, lymph node metastases, multifocality, vascular invasion, high levels of CA 19-9, incomplete capsule formation, and a resection margin of <2 cm.[15,54]

One study conducted using data from the Surveillance, Epidemiology, and End Results Program (SEER) database found that liver transplantation (LT) did not provide any survival benefit compared with minor or major hepatectomy in 465 patients with cHCC-CCA.[55] Analysis of the United Network for Organ Sharing (UNOS) database also indicated that LT had worse outcomes for cHCC-CCA patients compared with those with HCC.[56] However, a recent multicenter study showed that regardless of tumor burden, cHCC-CCA tumors that were treated by LT had significantly better overall survival and disease-free survival compared with resection.[45] In cases where cHCC-CCA was within the Milan criteria, LT was associated with improved disease-free survival compared to resection (5-year overall survival 70.3% vs. 33.6%, $p<0.001$).[45] Other studies have also suggested that patients with small tumors (<2 cm) and well- or moderately differentiated cHCC-CCA may benefit from LT with a low risk of post-transplant recurrence.[46,57] Though long representing an absolute contraindication for LT, recent studies have showed that ICC may be a potentially feasible option for early-stage disease (i.e.≤2 cm), with survival outcomes comparable to those of HCC.[58,59] In the USA there have been discussions about granting exception points to these patients. However, no definitive conclusions have been reached regarding the indication of LT for cHCC-CCA.

TACE is a viable treatment option for advanced or recurrent HCC. The effectiveness of TACE in treating unresectable cHCC-CCA is reported to dependent on the vascularity of the tumor. Hypervascular tumors have shown an response rate (>50% tumor necrosis) of 85%, while hypovascular tumors have only a response rate of 10%.[60] Postoperative adjuvant TACE has been found to have no impact on the recurrence-free survival or overall survival of cHCC-CCA.[61] A systematic review has suggested that drug-eluting bead (DEB)-TACE may be superior to conventional TACE in treating HCC, having better survival and treatment response outcomes when

appropriately selected.[62] However, currently there are no reports on the use of DEB-TACE for unresectable cHCC-CCA. Transarterial radioembolization (RE) with yttrium-90 microspheres has emerged as a promising liver-directed treatment for both HCC and ICC.[63,64] In patients with unresectable advanced cHCC-CCA, RE has shown a high disease control rate, with a partial response of 60% and a stable disease rate of 40%. The median overall survival from the time of the first RE treatment was reported to be 10.2 months.[65] Another study on RE for cHCC-CCA reported a response rate of 55% and a disease control rate of 65%.[66] RE appears to be a viable option for locoregional control of cHCC-CCA. Other local treatment modalities such as radiofrequency ablation and percutaneous ethanol injection have been reported for the treatment of cHCC-CCA, but the available data on the benefits of these interventions are inconclusive.[67]

Currently, there is a lack of evidence supporting effective systemic therapy for patients with advanced cHCC-CCA. Treatment decisions for these patients are frequently based on treatments for HCC and ICC.[68] A study by Kim *et al*.[69] suggested that HCC- and ICC-oriented treatment strategies yielded similar outcomes for patients with cHCC-CCA. Sorafenib, a commonly used targeted therapy for advanced HCC, and gemcitabine and cisplatin, an effective regimen for ICC, have been found to be ineffective for cHCC-CCA.[70] When compared as first-line treatments for advanced cHCC-CCA, chemotherapy had a higher objective response rate (ORR 8% vs. 0%) and disease control rate (DCR 24% vs. 19%) than sorafenib. The median overall survival was also better in the cytotoxic chemotherapy group (15.5 months vs. 5.3 months).[71] Currently, combination regimens with anti-programmed cell death protein 1/anti-programmed cell death-ligand 1 and antiangiogenic agents are being extensively tested for advanced HCC/ICC and show promising results.[72] Patients with cHCC-CCA may also be candidates for immunotherapy, as immune checkpoint inhibitors (ICIs) are effective in both HCC and ICC. A total of five patients received ICI-based systemic therapies achieved a promising ORR of 20% and a response duration of 11.6 months.[73] These findings strongly suggest that ICI-based regimens should be further evaluated in cHCC-CCA patients.

The prognosis of cHCC-CCA is generally poor, with reported outcomes being between those of HCC and ICC or worse than both.[74] One study indicated that the prognosis is primarily influenced by the ICC component.[33] However, the reported prognosis of cHCC-CCA in the existing literature is inconsistent, largely because of discrepancies in diagnostic criteria, which have only recently been clearly defined. Additionally, there is currently no established staging system specifically for cHCC-CCA. In the eighth edition (2017) of the American Joint Committee on Cancer (AJCC) tumor staging system, cHCC-CCA and ICC are staged in the same manner.[35] However, Zhou *et al*.[47] found that in contrast to the TNM for ICC, the TNM staging system for HCC correlated with overall survival and disease-free survival in a cohort of 206 cHCC-CCA patients. In addition, He *et al*.[75] supported the use of TNM staging for HCC to stratify the prognosis of cHCC-CCA patients undergoing resection. Developing a dedicated staging system for cHCC-CCA is crucial for guiding the therapeutic strategies. Further studies will elaborate upon the efficacy and accuracy of the alternative stratification system.

Perspective

cHCC-CCA is a rare but highly complex subtype of primary liver cancer. It shares clinical characteristics with both HCC and ICC, which poses a diagnostic challenge for clinicians and pathologists. The fifth WHO classification provided a definitive definition and diagnostic criteria for cHCC-CCA, but it is still necessary to identify specific biomarkers that aid in its detection. Primary liver cancer–derived organoids, which retain histological and genomic features of the original tumor, show promise as a means for targeted molecular therapies. Further research is needed to assess the efficacy of systemic chemotherapy and immunotherapy in treating advanced cHCC-CCA. Deep learning techniques applied to digital pathology analysis may offer potential solutions to various clinical inquiries, such as understanding the biology of the disease, making accurate diagnoses, and predicting treatment outcomes.[76]

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Conception and revision (XQJ, KH); Provision and interpretation of pathology (HW); Manuscript writing (KJC, YK); Final approval of manuscript (all authors).

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