Review

Current update on combined hepatocellular-cholangiocarcinoma

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Received 16 July 2014; accepted 22 July 2014
Available online 6 September 2014

Abstract

Combined hepatocellular-cholangiocarcinoma is a rare but unique primary hepatic tumor with characteristic histology and tumor biology. Recent development in genetics and molecular biology support the fact that combined hepatocellular-cholangiocarcinoma is closely linked with cholangiocarcinoma, rather than hepatocellular carcinoma.

Combined hepatocellular cholangiocarcinoma tends to present with an more aggressive behavior and a poorer prognosis than either hepatocellular carcinoma or cholangiocarcinoma. An accurate preoperative diagnosis and aggressive treatment planning can play crucial roles in appropriate patient management.

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Keywords: Cholangiocarcinoma; Cirrhosis; Computed tomography; Hepatocellular carcinoma; Magnetic resonance imaging

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http://dx.doi.org/10.1016/j.ejro.2014.07.001
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1. Introduction

Combined hepatocellular-cholangiocarcinoma (cHCC-CC) is a rare variant of primary hepatic cancer, with the reported incidence of this tumor varying between 0.4 and 4.7% [1–4]. However, as histopathological confirmation is not necessary to diagnose HCCs and vast majority of HCCs are diagnosed based on imaging findings, the projected incidences of cHCC-CC may not be accurate.

The first comprehensive review and histopathologic classification of cHCC-CC was given by Allen and Lisa in 1949 [1].

According to the World Health Organization (WHO), a definitive histopathological diagnosis of cHCC-CC requires demonstration of unequivocally differentiated hepatocellular and biliary components in the tumor [5].

The natural history of this rare cancer remains unclear. Most of the initial studies originated on the Asian subcontinent and supported the idea that this rare entity of hepatic malignancy is intimately related to hepatocellular carcinoma (HCC) and follows identical demographics and clinical presentation [6,7]. However, certain scattered Western studies reinforced a profile similar to cholangiocarcinoma [2,4]. More recent studies have exhibited a genetic, demographic and clinical profile that is intermediate between CC and HCC [8].

Regardless of its ambiguous natural history, cHCC-CC tends to present with a more aggressive behavior and poorer prognosis than either HCC or CC [7,9]. This aggressive behavior of the tumor can be attributed to propensities for vascular invasion, relatively large tumor size, regional adenopathy and satellite lesions [2,6,10]. Due to a dismal long-term prognosis, an accurate preoperative diagnosis and aggressive treatment planning can play crucial roles in appropriate patient management.

We present a contemporary and comprehensive review of this rare but unique primary hepatic malignancy with an overview of its natural history, recent advances in genetics and molecular biology, histopathogenesis, imaging and diagnosis.

2. Epidemiology and clinical features

A clear benchmark for the demographic and clinical profile of this rare cancer remains elusive.

Most of the initial studies advocated numerous resemblances between cHCC-CC and HCC. These studies suggested a similar patient profile including a strong male predominance, elevated serum AFP, and associated underlying cirrhosis (40%) and/or hepatitis (70%) and regarded cHCC-CC as an HCC variant [2]; most of these studies were from Asia [7,11–17].

Later, a few Western studies instead demonstrated demographic, clinical, and pathologic features similar to that of CC, including absence of HCC risk factors such as cirrhosis or hepatitis, no gender predominance, and normal serum AFP [2,4,18]. The situation became even more ambiguous when some of the more recent Western studies demonstrated clinical and demographic features intermediate to that of HCC and CC. Recent research has supported this fact: Risk factors for HCC were found in 10% of CC, 66% of cHCC-CC, and 83% of HCC, and cirrhosis was noted in 0% of CC, 20% of cHCC-CC, and 54% of HCC patients. Strong male predominance (14:1) remained a non-variable feature [8].

These variations in patient profile are difficult to explain, but may relate not only to histogenetic variation based on race, but also to disparate environmental carcinogenic factors, given different geographic locales.

3. Classification

chHCC-CC can be classified pathologically as well as genetically.

The earliest comprehensive pathologic classification was given by Allen and Lisa in 1949 and consisted of 3 subtypes: type A, characterized by synchronous, separate and autonomous epicenters of HCC and CC in one liver; type B, comprised of closely admixing distinguished foci of HCC and CC; and type C, consisting of truly combined HCC and CC components originating from the same tumor [1].

In the 1980s, Goodman proposed another classification encompassing three subtypes: (a) type 1 (or collision tumor): synchronous or metachronous occurrence of distinct epicenters of HCC and CC in the same liver, which collide each other; (b) type 2 (or transitional tumor): intimate intermingling of two components with actual transition of HCC elements to CC elements in the same tumor; and (c) type 3 (or fibrolamellar tumor): similar to a fibrolamellar HCC, but with mucin-producing pseudoglands [4].

Lisa and Allen’s type C is the equivalent of Goodman’s type 2 (transitional tumor), and both of these types most closely fit the current WHO criteria, which define chHCC-CC as intimately mixed elements of fully differentiated hepatocellular carcinoma (HCC) and cholangiocarcinoma (CC) components with identification of transitional or intermediate areas [5]. To avoid unnecessary confusion, only WHO classification should be followed.

4. Immunohistopathology

As histopathology remains the only avenue for definitive diagnosis, the biopsy sample must show clear evidence of both hepatocellular and biliary differentiation of monoclonal origin,
with the respective tumor cells intermingling intimately [5]. Signs of HCC differentiation would include bile production and bile canaliculi as well as a pseudoglandular or trabecular growth pattern, whereas signs of CC differentiation would include mucin-producing biliary epithelium forming true glandular structures surrounded by desmoplastic stroma (Fig. 1d and e and Fig. 2h) [19]. Moreover, the tumor must also satisfy the typical immunohistochemical stains of both HCC and CC and should always be in the differential diagnosis if there are immunophenotypical features of both CC and HCC within the lesion [20]. Exclusion of collision tumor, e.g., separate foci of CC and HCC without intimate mixing, is obligatory, as this would not be considered a true cHCC-CC.

Biliary cell stains include mucin, CK7, and CK19, while hepatocellular stains comprise polyclonal CEA, Hep Par 1, and CD10 (Fig. 2g). The newly introduced hepatocellular marker glypican-3 is highly sensitive and specific for identification of HCC component and only weakly reactive with CC [3,21].

Proper sampling targeting the transitional areas is vital for accurate immunohistological diagnosis.

However, despite accurate sampling, accurate pre-operative diagnosis might be thwarted by certain pitfalls in immunohistochemical analysis [3]. For example, one can misinterpret the pseudoglandular structure of HCC for the true glandular structures of CC; here, mucin staining would be useful [3]. Additionally, CK7 and CK19 may not be entirely specific for CC, as it can be expressed in HCC as well [22]. Finally, immunohistochemical staining is not useful in differentiating the inflammatory biliary ductal reactivity usually present with HCC from the malignant biliary epithelium of true CC. One differential factor to avoid this hazard would be that a true CC component would demonstrate desmoplastic stroma rather than the inflammatory cells of ductal reactivity [3].

5. Genetics and molecular analysis

Classically HCC demonstrates certain peculiar genetic alterations including loss of heterozygosity (LOH) at chromosomes 8p, 17p, 4q, 1p, 16q, 13q, 6q, 16p, and 9p. Additionally, inactivation of tumor suppressor genes like TP53, and activation of oncogenes like CTNNB1/β-catenin (and the Wnt pathway) has been implicated in the etiopathogenesis of HCC. On the other hand, a microsatellite instability (MSI-H) phenotype, TP53 and KRAS2 mutations have been described in CC. However, sparse information about the genetics and molecular biology of chCC-CC is available in the literature.

Genome-wide typing has demonstrated higher incidences of LOH at chromosomes 3p and 14q in cHCC-CC and CC and can be taken as specific to these tumors [8]. Tumor suppressor gene RASSF1 (part of the ras signaling pathway) is located in the

Fig. 1. 59-Year-old man with chronic hepatitis B. (a) Axial CT (arterial phase): hypodense mass is seen in the right hepatic lobe (circle). Note incidental cholelithiasis. (b) Venous phase: foci of peripheral enhancement in the hypodense mass (arrow). (c) Equilibrium phase: the mass demonstrates central enhancement in the delayed phase (asterisk) surrounded by hypodense rim (large arrow). Washout is evident in the previously seen peripheral enhancing foci (small arrow). (d and e) H&E stain images at 4× and 10× magnifications showing malignant cells of hepatocellular carcinoma (figure d, asterisk) seen alongside malignant cells of cholangiocarcinoma (figure d, box). The diagnosis was consistent with CC dominant cHCC-CC.
Fig. 2. 42-Year-old-Vietnamese woman with history of hepatitis. (a) Axial T1w in-phase image shows hypointense mass in right hepatic lobe (arrow). (b) Axial T1w opposed-phase image shows no signal drop, which rules out presence of (microscopic) fat (therefore adenoma or well differentiated HCC). (c) Axial T2w image shows peripheral rind of intermediate signal intensity (arrow) with central hypointensity (asterisk). Scattered foci of hyperintensity centrally (small arrow). (d) Arterial phase shows peripheral enhancement of the mass (arrow) with minimally enhancing central component (asterisk). (e) Venous phase demonstrates washout in the periphery (arrow) and progressively enhancing central component which corresponds to fibrosis within the CC component at subsequent histopathology (asterisk). (f) Equilibrium phase shows persistent central enhancement (asterisk). (g) H&E stain images at 4× magnifications showing mixed components. (h) CD10 antibody staining protocol for immunohistochemistry. (i) Glypican-3 staining highlighting the HCC component.
region of 3p LOH [23]. However, no definitive tumor suppressor gene has been found in the region of 14q LOH. Potentially, LOH at 3p and 14q could also be exploited to discriminate between hepatocellular and biliary differentiation of the tumor.

Mutation of tumor suppressor gene TP53 cannot be correlated with tumor differentiation in primary hepatic tumors, as it is seen in 11% of CC, 27% of cHCC-CC, and 26% of HCC [8]. However, detection of the activation of the CTNNB1/β-catenin oncogene may be helpful, given that this mutation is found in 20% of HCC but is not found in cHCC-CC or CC [8,24].

It is apparent that analysis of certain genetic signatures may not only help differentiate these tumors, but will also promote further genetic analysis to better understand genetic variations and ultimately the disparities in clinical presentation and prognosis. Extensive studies are needed to further explore the genetic alterations specific to cHCC-CC.

6. Histogenesis

While the cell of origin of this cancer remains controversial, genetic and molecular analysis have been instrumental in furthering theories of histogenesis. Given the known bidirectional differentiation potential of both hepatocytes and biliary epithelium in rat models and humans, it has been postulated that the cell of origin is either a dedifferentiated CC or HCC or, more likely, a transitional or intermediate hepatic progenitor cell [4,25].

Using microdissection and DNA extraction, Fuji et al. observed 3 tumor types based on LOH patterns: type 1, a collision tumor of two truly independent clones; type 2, a homogeneous bidirectional (hepatic and biliary) monoclonal; and type 3, a bidirectional monoclonal, but with histologic diversity as a result of subclones, with probable overlap of types 2 and 3. This demonstration of common allelic losses in each element of the lesion strongly supports the hypothesis that these cancers are of monoclonal origin with bidirectional phenotypic differentiation [26].

7. Imaging

Given the poorer prognosis of cHCC-CC compared to HCC or CC, accurate pretreatment diagnosis is critical because it can alter management decisions.

Imaging features of cHCC-CC are scarcely described in the literature. Awareness of characteristic imaging features of cHCC-CC may enable a radiologist to identify or screen these tumors pre-operatively and perform image-guided biopsies.

7.1. Ultrasound

The sonographic appearance of cHCC-CC is non-specific; it may demonstrate a target appearance consisting of a round hypoechoic mass with a central hyperechoic focus or a heterogeneous hypoechoic mass. Heterogeneity likely reflects histologic diversity [27]. However, ultrasound could be a useful tool to get a targeted image-guided sample from a suspicious mass.

7.2. CT

On non-contrast computed tomography (CT), cHCC-CC demonstrates a non-specific appearance and appears hypodense or isodense to liver parenchyma.

On contrast-enhanced CT a variable pattern of enhancement has been described. The pattern of enhancement is governed not only by the proportion and distribution of the CC vs. HCC component, but also by the gamut of histological patterns of CC. Different histologic subtypes of CC have been shown to have varying enhancement patterns. The medullary type demonstrates early phase enhancement, whereas the scirrhouss type shows late-phase enhancement. On the other hand, the HCC component shows early hyper-enhancement and delayed washout.

Different researchers have made efforts to classify cHCC-CC according to their enhancement patterns. Aoki et al. described two types of CT enhancement patterns [13]: (1) Type A: This subtype demonstrates a peripheral enhancement in the early phase with central hyperenhancement and peripheral washout on the delayed phase. This pattern can be explained by concentric zones of HCC peripherally and CC centrally, with associated transitional zones in between; (2) Type B: This subtype closely follows the enhancement demonstrated by classical HCC (diffuse early hyperenhancement and diffuse washout on delayed phase).

Sanada et al. identified three enhancement patterns [28]: (1) Type I: Early hyperenhancement followed by washout in the delayed phase; (2) Type II: Peripheral enhancement in both the early and delayed phases; and (3) Type III: Two distinctive enhancement patterns in the same tumor, one following the typical HCC pattern (early enhancement with delayed-phase washout) and the second imitating CC (delayed enhancement on late imaging).

It is apparent from the description that Aoki’s type B and Sanada’s type I follow the typical HCC pattern and would most certainly result in a preoperative imaging diagnosis of HCC rather than cHCC-CC or CC [28]. Histologically, these tumors are HCC-predominant lesions.

Sanada’s type III, similar to Aoki’s type A, is the most suggestive of cHCC-CC on imaging. This is a combination of typical imaging features of both HCC and CC, and manifestation of this pattern on imaging should immediately raise suspicion, regardless of the clinical presentation or serum tumor markers [28]. Histologically, these tumors are comprised of both HCC and CC components (Fig. 1a–e).

Sanada’s type II pattern remains atypical and can be explained by the presence of central fibrotic or necrotic components attached to a peripheral cHCC-CC component.

7.3. MRI

MRI features of cHCC-CC have not been described extensively. To the best of our knowledge, less than ten studies have been published at the time of writing this article [29–34].

The cHCC-CC may appear hypointense on T1w images (Fig. 2a and b). On T2w images, they usually demonstrate intermediate to high signal intensity with or without central
hypointense focus, which corresponds to a central CC or fibrotic component (Fig. 2c).

On dynamic imaging, the enhancement patterns usually follow patterns similar to those described by Aoki and Sanada on CT imaging (Fig. 2d and f) [33,35]. More recently, de Campos et al. have also described features of MR imaging that were variations on Sanada’s descriptions: early ring enhancement with progressive enhancement centrally, or heterogeneous early enhancement with partial washout [34].

MR imaging with a hepatocellular agent like gadoxetic acid may also be useful to differentiate cHCC-CC and CC. Gadoxetic acid has both perfusion and hepatocyte-selective features and is highly liver-specific, with about 50% of the dose taken up by hepatocytes as early as one minute after injection. Hepatobiliary phase imaging can then be done 10–20 min after injection in conjunction with dynamic phase imaging earlier. Characterization of lesions on routine MR with standard extracellular agents is based on precontrast signal characteristics as well as the postcontrast perfusion pattern; dual function contrast agents, however, allow characterization with all of these features as well as cellular differentiation because of the hepatocyte selectivity, which has typically required histopathology. In the setting of cHCC-CC, the various appearances of this lesion may not necessarily relate to hepatocyte selectivity, however, but regardless can result in specific patterns which are suggestive [35]. For example, Hwang retrospectively evaluated gadoxetic acid-enhanced MR images of a pathologically proven series of 20 cases of CC and 20 cases of cHCC-CC to assess for imaging discriminators [36]. Their data suggested that a lobular shape, weak rim enhancement, and a complete target appearance favored CC, while an irregular shape, strong peripheral enhancement and absence of the target sign favored cHCC-CC, particularly the HCC predominant type.

8. Differential diagnosis

Classical imaging pattern of cHCC-CC may closely resemble metastasis [34]. Both hypervascular and hypovascular metastases share this pattern, particularly on MR imaging [37]. Diagnostic consideration of metastasis should be considered more likely in a patient without underlying liver disease even without history of known primary malignancy, given the rarity of cHCC-CC [34,37]. Other discriminators in favor of metastases include multiple lesions or central necrosis. Hepatocyte-selective imaging on MR with gadoxetic acid will also differentiate a metastasis from cHCC-CC, with the metastasis typically non-enhancing on the hepatobiliary phase [35]. A quick reference of cHCC-CC versus metastasis has been depicted in Table 1. In a patient with chronic underlying liver disease, metastases are less likely, so this pattern would more strongly suggest cHCC-CC. However, very aggressive HCC has also been shown to have this particular ring-like enhancement pattern and thus should also be considered [38].

Other enhancement patterns of cHCC-CC are much less specific. A histopathologically HCC-predominant cHCC-CC with early uniform hyperenhancement and delayed washout will reasonably be described preoperatively as an HCC in a liver with underlying chronic disease, while in a liver without underlying disease, the differential diagnosis would include HCC, adenoma, FNH, and hypervascular metastasis [34,39]. Willekens et al. have reported one case of a pathologically proven cHCC-CC that had the typical appearance of FNH on MRI, including early phase enhancement and delayed enhancement of a central scar, which can mimic chCC-CC [33]. One discriminator is the T1w appearance, as cHCC-CC can appear hypointense, while FNH will be iso- or hyperintense. Additionally, given that FNH is hepatocellular in origin, gadoxetic acid imaging with MR during the hepatocyte-selective phase will demonstrate typical enhancement of the entire lesion, unlike cHCC-CC [35,36].

Histopathologically CC-predominant cHCC-CC lesions that demonstrate minimal early peripheral enhancement and strong central enhancement on delayed imaging will likely be described as CC at CT or MR imaging. While it is very difficult to differentiate these two cancers, a complete target appearance on the hepatobiliary phase of gadoxetic acid imaging is more suggestive of CC than CC-predominant cHCC-CC [36].

Serum tumor marker levels should always be correlated with the imaging appearance to increase the accuracy of the preoperative differential diagnosis [34].

9. Treatment and prognosis

The prognosis of cHCC-CC is dismal, even with resection. Various prognostic factors described in different studies

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**Table 1**

| Differential diagnosis of cHCC-CC. |
|-----------------------------------|-----------------|-----------------|
| **Underlying liver disease**      | **cHCC-CC**     | **Metastasis**  |
| T1w                               | Common          | Unusual         |
| T2w                               | Hypointense     | Usually hypointense |
| Arterial phase                     | Intermediate SI +/- central hypointensity | Moderate-marked hyperintense |
| Equilibrium phase                  | Varies according to dominant histological component but classically contains area of hypervascularity | Variable according to the primary but ring-like hyperintensity can be seen |
| Gadoxetic acid (hepatobiliary phase) | Area of contrast retention | May demonstrate fill in or become hypointense to parenchyma |
| Multiplicity                       | Partial or complete target appearance | No contrast retention |
| Central necrosis                   | –               | Often           |
|                                   | –               | May present     |
like tumor size, presence of satellite nodules and lymph nodal involvement are not definitive. Early reports demonstrated that in cHCC-CC, tumor size (median 8.8 cm), presence of satellite tumors (29%), and incidence of vascular invasion and lymph node involvement were not significantly different statistically compared to CC or HCC [2]. Other studies reported significantly increased lymph node involvement and vascular invasion as well as poorer overall survival when compared to HCC, although these were all similar to CC [6,10]. Additionally, multifocal disease and decreased capsular formation in cHCC-CC were regarded as signs of more aggressive behavior compared to HCC [14,40]. Early reports stated that tumor stage, size, vascular invasion, and multifocality were poor prognostic indicators [14,41], while a more recent study has indicated that an elevated CA 19-9 level was the only statistically significant indicator of poor survival [40].

While resection with node dissection is the only curative option [40], contemporary evidence is that prognosis after resection is worse than CC or HCC [7,9]. One such study assessed median time-to-recurrence (TTR) and overall survival (OS) after curative resection in cHCC-CC, CC, and HCC: median TTR and OS for cHCC-CC were 5.4 and 18 months, both significantly shorter than CC or HCC [9]. Additionally, 5-year survival rates have been reported at 23–24%, lower than either CC or HCC [20,40].

Despite the poor prognosis regardless of current treatment modalities, it must be emphasized that the correct diagnosis is still necessary. Treating cHCC-CC as with the typical management for either CC or HCC will not allow further studies exploring more comprehensive multimodality treatments, including extended hepatectomy, regional node dissection and adjuvant therapy. Regional treatments such as transarterial chemoembolization (TACE) are theoretically not an ideal treatment option because the fibrotic CC component of cHCC-CC will have relatively poor uptake of therapeutic agents, but localized treatments such as TACE and RFA have been attempted as part of a multimodality approach for recurrent disease [40,42]. Liver transplant or radioembolization should also be assessed, as their role currently remains uncertain in this disease [16,43].

10. Making the pre-operative diagnosis

While the complex nature of this cancer makes specific imaging diagnosis difficult, the radiologist should suggest this diagnosis and prompt an expanded preoperative image-guided biopsy by assessing the imaging findings in conjunction with serum tumor markers [11,34,44,45]. The expanded biopsy should be more comprehensive than a typical biopsy, and try to include some of the transitional areas noted on the imaging study.

The combination of imaging features and tumor markers (CA 19-9 and AFP) could be useful in screening cHCC-CC and prompting for an image-guided biopsy (Fig. 3). The diagnosis of cHCC-CC should be strongly considered in the following circumstances (Fig. 4):

1. If the lesion demonstrates imaging features of both CC and HCC, regardless of marker levels.
2. If both AFP and CA 19-9 are elevated, regardless of imaging appearance.
3. If the imaging appearance contradicts the tumor marker, e.g., typical HCC enhancement pattern with elevated CA 19-9 or conventional CC enhancement pattern with abnormal AFP.

Post-biopsy, the diagnosis is made based on immunohistopathological features.

11. Conclusion

Because of its rare occurrence, gamut of demographic and clinical profiles, ambiguous imaging features, and inconsistent application of histopathologic criteria, preoperative diagnosis of cHCC-CC remains challenging. Nevertheless, the pre-operative diagnosis remains critical due to its aggressive nature and poor prognosis in comparison to HCC and CC. A combination of certain imaging features and levels of serum tumor markers facilitates a high level of suspicion, prompting a carefully targeted (sampling some of the transitional areas noted on the
imaging study) extended biopsy. The final diagnosis of cHCC-CC is based on immunohistopathology, special stains, and genetic analysis and allows appropriate and aggressive treatment planning. Continued investigation and research are required to establish the roles of both advanced imaging and molecular analysis in the diagnosis, classification, and treatment of cHCC-CC.

**Disclosure**

None declared.

**Conflict of interest**

None declared.

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