

The Growing Interest in the Combined Hepatocellular-intrahepatic Cholangiocarcinoma (cHCC-CCA)

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Combined hepatocellular-cholangiocarcinoma (cHCC-CCA) is a rare primary liver cancer displaying both hepatocytic and cholangiocytic differentiation. This combined tumor has about 1% incidence among primary hepatic cancers, a more aggressive behaviour and a poorer prognosis as compared to hepatocellular carcinoma (HCC). While keeping the proportion of 1% among primary liver cancers, the cHCC-CCA incidence is increasing. A systematic review and meta-analysis of 53 epidemiological studies performed both in Western and Asian countries between 2008 and 2019 demonstrated that cHCC-CCA incidence had increased in this period with an annual percentage change (APC) of + 4% as compared to HCC (APC + 2.6%) [1]. The increase occurred mainly in Western countries, whereas trends decreased in the Asian region, although still remaining high.

The etiology of the combined tumor is the same as that of its components. Geographic variations in CCA incidence are related to the variations in risk factors. Classical risk factors for HCC and CCA seem also to predispose to the development of cHCC-CCA. In the context of a better control of viral B and C infections, the increased risk of primary liver cancers should probably be related to the worldwide increase in the prevalence of metabolic

disorders (obesity, type II diabetes mellitus and non-alcoholic fatty liver disease – NAFLD) [2].

The pathological definition of cHCC-CCA has significantly evolved over time; however, the diagnosis of this combined tumor remains challenging for radiologists and especially for pathologists, with biopsy specimens.

The combined tumors were first introduced in the WHO classification of the diseases (4th edition, 2010), which a short time afterwards, was modified in the 5th WHO classification (2019) [3]. This new version of the histological classification system no longer recognizes subtypes of cHCC-CCA with stem cell features, which have been recategorized as either HCCs or intrahepatic cholangiocarcinomas (iCCAs). The intermediate cell carcinoma was introduced as a specific subtype and cholangiolocarcinoma as a subtype of cholangiocellular carcinoma. The gold standard for diagnosis is the histology of surgical specimens [4]. The presence of CCA elements in the tumor can be confirmed with cytokeratin 19 (CK19) and cytokeratin 7 (CK7) staining by immunohistochemistry.

The 2019 WHO classification highlighted that the diagnosis of cHCC-CCA should be primarily based on morphology using routine stainings, with additional immunostaining to refine identification of subtypes. The 2014 *Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma* recommended specific immunostaining for detecting markers of HCC or progenitor cells thus distinguishing cHCC-CCA from iCCA tumors „only if this information will change management” (Recommendation B1) [5]. This recommendation remains current. Immunohistochemical markers may be applied, but still have limited value for the diagnosis of cHCC-CCA.

The imaging appearance of these tumors may overlap with that of HCC and CCA and discriminating features such as classic enhancement patterns and biliary ductal dilation are not universally present. The Liver Imaging Reporting and Data System (LI-RADS) category enables the correct classification of most HCCs and intrahepatic CCAs, whereas differentiation of combined cHCC-CCA from HCC is often unreliable [6]. But magnetic resonance imaging LI-RADS may evaluate the HCC component in the combined tumor. It was recently found that a higher than 65% HCC component in association with a high level of serum carcinoembryonic antigen (CEA) can result in a better overall survival for these patients [7].

The therapeutic options are challenging due to the dual nature of the neoplastic cells. In patients with iCCA, surgery or locoregional therapy [transarterial chemoembolization (TACE)] and adjuvant chemotherapy are recommended, according to the patient status [8]. In patients with cHCC-CCA, surgical resection with lymph node dissection is presently the only curative option [9], and remains the preferred option in resectable patients. The risk of recurrence, however, is high, especially in comparison with other primary liver cancers such as HCC. Due to the presence of comorbid liver dysfunction, the *NCCN Guidelines for Hepatobiliary Cancers* consider a multidisciplinary evaluation as being essential for an optimal treatment strategy [10].

Development of an efficient therapeutic strategy for the combined tumor is presently evaluated in many clinical trials. Liver transplantation is the standard for patients with unresectable HCC, but its role in cHCC-CC patients is still controversial [11]. Liver transplantation may be applied in these patients in cases of advanced cirrhosis. Within the Milan criteria, liver transplant for cHCC-CCA and HCC was shown to result in similar overall survival, justifying consideration of transplantation in these traditionally difficult to treat patients [12].

The growing interest in this heterogeneous class of tumors, difficult to be diagnosed and with limited therapeutic options available, has been proved by the numerous studies published in recent years, including the recent *Expert European Consensus Statement* [13]. Analysis of series of patients from different parts of the world will hopefully help to better understand the cHCC-CCA biology and its diagnosis. A multidisciplinary approach integrating genomic, functional and clinicopathologic characteristics is mandatory to identify targeted therapies for this long-time considered orphan disease.

In this issue of the *Journal of Gastrointestinal and Liver Diseases*, Teufel and collab. report a very large European population-based registry of liver tumors [14]. A series of 9,134 adult patients were diagnosed by histology between 2009 and 2020 in a German Clinical Cancer Registry database as HCC, iCCA and cHCC-CCA. The authors found that the combined liver tumor was diagnosed in 166 patients (1.8% prevalence among the primary hepatic tumors). As in most published series [13, 15, 16], patients with cHCC-CCA in this series were mostly males, aged over 65 years. In many aspects, the combined tumors had more similarities with iCCA than with HCC. The progress-free time after diagnosis was shorter than that of iCCA or HCC. This might be because patients with cHCC-CCA were mainly diagnosed in the advanced stage (IV) of the disease, explaining the shorter survival after diagnosis. The overall survival and local recurrence-free survival rates of cHCC-CCA were between those of HCC and CCA rates, similar to series from Europe and America [2, 13] and from Asia [15, 16].

In the German series, HCC diagnosis was performed clinically in most (78%) cases, while diagnosis of cHCC-CCA and iCCA was obtained exclusively from the pathology report. Nowadays, diagnosis of HCC is frequently made with imaging alone, without biopsy, and management decisions, including organ allocation for transplantation for unresectable HCC rely upon the radiological diagnosis [17].

However, for iCCA or cHCC-CCA, biopsy still remains the key for diagnosis. Accordingly, Teufel and collab. accept

that some cases of cHCC-CCA or iCCA might have been overlooked in their series, in the absence of tumor biopsy.

The patients with cHCC-CCA, for whom information was available to the authors, were mainly treated by surgical resection or TACE as first line therapy. They had a better survival than those who received only systemic chemotherapy.

In conclusion, the excellent study by Teufel et al. adds valuable information regarding the clinical outcome of the combined tumors, also confirming that biopsy of a liver tumor with unreliable radiological aspect is mandatory. This would allow a correct diagnosis and will help to identify the best treatment options. So far, for these tumors, we have more questions than answers.

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