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Cholangiocarcinoma 2020: the next horizon in mechanisms and management

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Abstract | Cholangiocarcinoma (CCA) includes a cluster of highly heterogeneous biliary malignant tumours that can arise at any point of the biliary tree. Their incidence is increasing globally, currently accounting for ~15% of all primary liver cancers and ~3% of gastrointestinal malignancies. The silent presentation of these tumours combined with their highly aggressive nature and refractoriness to chemotherapy contribute to their alarming mortality, representing ~2% of all cancer-related deaths worldwide yearly. The current diagnosis of CCA by non-invasive approaches is not accurate enough, and histological confirmation is necessary. Furthermore, the high heterogeneity of CCAs at the genomic, epigenetic and molecular levels severely compromises the efficacy of the available therapies. In the past decade, increasing efforts have been made to understand the complexity of these tumours and to develop new diagnostic tools and therapies that might help to improve patient outcomes. In this expert Consensus Statement, which is endorsed by the European Network for the Study of Cholangiocarcinoma, we aim to summarize and critically discuss the latest advances in CCA, mostly focusing on classification, cells of origin, genetic and epigenetic abnormalities, molecular alterations, biomarker discovery and treatments. Furthermore, the horizon of CCA for the next decade from 2020 onwards is highlighted.

Cholangiocarcinoma (CCA) constitutes a diverse group of malignancies emerging in the biliary tree. CCAs are divided into three subtypes depending on their anatomical site of origin: intrahepatic (iCCA), perihilar (pCCA) and distal (dCCA) CCA[1,2] (FIG. 1). Of note, considered as an independent entity, mixed HCC–CCA tumours are a rare type of liver malignancy sharing features of both iCCA and HCC and presenting an aggressive disease course and poor prognosis[3,4]. iCCAs arise above the second-order bile ducts, whereas the point of anatomical distinction between pCCA and dCCA is the insertion of the cystic duct. pCCA and dCCA can also be collectively referred to as 'extrahepatic' (eCCA)[5]. In the USA, pCCA is the single largest group, accounting for approximately 50–60% of all CCAs, followed by dCCA (20–30%) and iCCA (10–20%)[1,6,7]. CCA is the second most common primary hepatic malignancy after hepatocellular carcinoma (HCC), comprising approximately 15% of all primary liver tumours and 3% of gastrointestinal cancers[1,6,7]. CCAs are usually asymptomatic in early stages and, therefore, often diagnosed when the disease is already in advanced stages, which highly compromises therapeutic options, resulting in a dismal prognosis[1,8]. CCA is a rare cancer, but its incidence (0.3–6 per 100,000 inhabitants per year)[1] and mortality (1–6 per 100,000 inhabitants per year, globally[9], not taking into account specific regions with incidence >6 per 100,000 habitants such as South Korea, China and Thailand) have been increasing in the past few decades worldwide, representing a global health problem. Despite advances in

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