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Surveillance in cholangiocellular carcinoma

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A B S T R A C T

Cholangiocellular carcinoma is the most frequent malignant neoplasm originating from the epithelium of intra- or extrahepatic bile ducts. In the past decades, the incidence of cholangiocarcinoma has been shown to increase while overall mortality has remained high with an approximate 5-year overall survival below 20%. Surgery remains the only curative option while systemic treatment is limited to palliative chemotherapy. Therefore, surveillance strategies for patients at risk of developing cholangiocarcinoma are urgently needed, particularly in patients with primary sclerosing cholangitis and patients infected with liver flukes. Here we summarize the currently available data on surveillance of risk populations and methods for the detection of cholangiocarcinoma.

Classification and epidemiology of cholangiocarcinoma

Cholangiocellular carcinoma (CCA) accounts for approximately 10% of all malignant liver tumours and approximately 3% of all gastrointestinal tumours. In contrast to hepatocellular carcinoma, CCA arise from the epithelium of the bile duct and display a glandular growth type [1]. CCA are historically grouped according to their site of origin into intrahepatic cholangiocarcinoma (iCCA) and extrahepatic cholangiocarcinoma (eCCA), with the latter being further subdivided into perihilar Klatskin tumors (pCCA) and distal cholangiocellular carcinoma (dCCA) [2]. In most studies, pCCA represents the most frequent subtype whereas recent studies report a more prevalent iCCA subtype [3–6]. Gallbladder and papillary adenocarcinoma are usually considered separate entities although they are sometimes included into CCA trials.

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The incidence of cholangiocarcinoma has been reported to increase in the past decades in many parts of the world, including the United States, Europe and Asia [6–10] with only few exceptions [11]. Among the CCA subtypes, this increase in incidence is unequally distributed with most pronounced increases seen in intrahepatic cholangiocarcinoma [12–14] and only minor changes in the incidence of extrahepatic CCA. The exact reasons for this reported increase remain currently unclear as both an increased detection and a true increase in incidence are debated. Globally, CCA still represent a rare malignancy, affecting approximately 1–2/100.000 people, but with a very heterogenous distribution in different parts of the world. As an example, CCA incidence has been estimated at 0.1/100,000 in Australia but at more than 130/100,000 in parts of Asia (e.g. Khon Kaen Province in Thailand [15]). The unequal global distribution of CCA is mainly attributable to the presence of risk factors in some areas, e.g. endemic fluke infestation in Thailand and other Asian countries.

Despite the low incidence of CCA wordwide, CCAs are among the most lethal tumours due to the high mortality in the affected patients. Five years after the initial diagnosis, only 10–20% of CCA patients are still alive reflecting a very dismal prognosis of CCA patients in general. Despite improvements in both diagnosis and treatment, mortality rates have not changed significantly in the past decades. Most studies have reported a decrease in the mortality of pCCA and dCCA, but an increase for iCCA [3,4,6]. Surgery remains the only curative treatment option for patients so far, with most patients undergoing extensive liver resection and a limited number of patients who receiving liver grafts. Even after resection, the tumour recurs in 40–80% of the patients, highlighting the need for efficient means to improve the prognosis of patients suffering from this deadly disease.

Risk factors

Most cases of cholangiocellular carcinoma are not associated with genetic susceptibility, but develop in the context of chronic biliary inflammation. The clinical presentation of CCA is non-specific and insufficient to establish a diagnosis and patients with early stage disease are usually asymptomatic. Due to the chronic biliary inflammation, many patients eventually develop bilary obstruction and clinical symptoms due to cholestasis including pruritus.

Very recently, a population-based cohort study was performed to evaluate whether chronic pruritus could be an early marker of underlying malignancies. In this study, 8,744 patients with chronic pruritus were matched with 31,580 patients without chronic pruritus. The overall incidence of hematological malignancy and bilary cancer in patients with chronic pruritus was very low with 0.0016 and 0.0003 per person year indicating that broad screening for malignancy in patients with chronic pruritus without concomitant skin findings is not recommended [16].

Infection with the hepatobiliary flukes Clonorchis sinensis and Opisthorchis viverrini represents a prototypic inflammatory cause for the devealopment of cholangiocarcinoma in endemic areas and is responsible for the highest global frequencies of cholangiocarcinoma in Southeast Asia [15,17]. Chronic obstruction of bile ducts due to choledocholithiasis or hepatolithiasis has been described as a risk factor for CCA development [17].

In western countries, primary sclerosing cholangitis (PSC) is the major risk factor for CCA, affecting preferentially young patients. PSC prevalence ranges from less than 0.1/100.000 in Asia and Southern Europe [18,19] to 1.3/100.000 in Norway [20]. In PSC patients, the risk of death due to cancer has been reported as high as 44% [21], with an annual transformation rate of up to 1.0% per year [2,22]. Compared to the general population, the risk for the development of malignant disease is increased up to 1560-fold [21,23]. The development of cancer seems to be independent from the duration of the biliary inflammation, since CCA often develops in the first few years after PSC diagnosis [24,25]. In addition to primary sclerosing cholangitis, secondary sclerosing cholangitis represents a rare cause of cholangiocarcinoma [26].

Congenital fibropolycystic diseases of the bile duct system, including choledochal cysts, Caroli's disease and Caroli's syndrome [27] confer an increased risk for the development of CCA [28] with a reported life-time risk of approximately 10% in adults [28,29]. Similar to colorectal adenoma and pancreatic intrapapillary mucinous neoplasia, a possible role of premalignant lesions for CCA is debated. Among these, biliary intraepithelial neoplasm and intraductal papillary neoplasms are most frequently found in perihilar and distal CCA, while bile duct adenoma, biliary adenofibroma and von