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**REVIEW**

- 4252 Update on the association of hepatitis B with intrahepatic cholangiocarcinoma: Is there new evidence?  
*Fragkou N, Sideras L, Panas P, Emmanouilides C, Sinakos E*
- 4276 Viral infections in inflammatory bowel disease: Tips and tricks for correct management  
*Craviotto V, Furfaro F, Loy L, Zilli A, Peyrin-Biroulet L, Fiorino G, Danese S, Allocca M*
- 4298 Pancreatic cancer: A review of epidemiology, trend, and risk factors  
*Hu JX, Zhao CF, Chen WB, Liu QC, Li QW, Lin YY, Gao F*
- 4322 Minimally invasive image-guided therapy of primary and metastatic pancreatic cancer  
*Bibok A, Kim DW, Malafa M, Kis B*
- 4342 Comprehensive review of diagnostic modalities for early chronic pancreatitis  
*Ge QC, Dietrich CF, Bhutani MS, Zhang BZ, Zhang Y, Wang YD, Zhang JJ, Wu YF, Sun SY, Guo JT*

**MINIREVIEWS**

- 4358 Dysregulated liver function in SARS-CoV-2 infection: Current understanding and perspectives  
*Huang YK, Li YJ, Li B, Wang P, Wang QH*
- 4371 Impact of surgery for chronic pancreatitis on the risk of pancreatic cancer: Untying the Gordian knot  
*Kalayarasan R, Narayanan S, Sahoo J, Mohan P*
- 4383 Neoadjuvant therapy for pancreatic ductal adenocarcinoma: Opportunities for personalized cancer care  
*Hamad A, Brown ZJ, Ejaz AM, Dillhoff M, Cloyd JM*
- 4395 Role of artificial intelligence in multidisciplinary imaging diagnosis of gastrointestinal diseases  
*Berbis MA, Aneiros-Fernández J, Mendoza Olivares FJ, Nava E, Luna A*
- 4413 Hyperbaric oxygen therapy as a complementary treatment for radiation proctitis: Useless or useful? – A literature review  
*Alpuim Costa D, Amaro CE, Nunes A, Cardoso JS, Daniel PM, Rosa I, Branco JV*

**ORIGINAL ARTICLE****Retrospective Study**

- 4429 Multifocal autoimmune pancreatitis: A retrospective study in a single tertiary center of 26 patients with a 20-year literature review  
*Huang XM, Shi ZS, Ma CL*

- 4441** Recent trends in the prevalence and distribution of colonic diverticula in Japan evaluated using computed tomography colonography

*Isohata N, Nagata K, Utano K, Nozaki R, Nozu S, Kato T, Kijima S, Matsumoto H, Majima K, Ryu Y, Hirayama M, Endo S*

**Observational Study**

- 4453** Prognostic role of plasma level of angiotensin-1, angiotensin-2, and vascular endothelial growth factor in hepatocellular carcinoma

*Choi GH, Jang ES, Kim JW, Jeong SH*

**Prospective Study**

- 4468** Determinants of disease-specific knowledge among children with inflammatory bowel disease and their parents: A multicentre study

*Kowalska-Duplaga K, Gawlik-Scislo A, Krzesiek E, Jarocka-Cyrta E, Łazowska-Przeorek I, Duplaga M, Banaszkiwicz A*

**LETTER TO THE EDITOR**

- 4481** Is there higher percentage of undetected osteopenia and osteoporosis among patients with ulcerative colitis in Saudi Arabia?

*Olic Akrapovic I, Radic M, Tonkic A*

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## Update on the association of hepatitis B with intrahepatic cholangiocarcinoma: Is there new evidence?

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### Abstract

Intrahepatic cholangiocarcinoma (iCCA) is a subgroup of cholangiocarcinoma that accounts for about 10%-20% of the total cases. Infection with hepatitis B virus (HBV) is one of the most important predisposing factors leading to the formation of iCCA. It has been recently estimated based on abundant epidemiological data that the association between HBV infection and iCCA is strong with an odds ratio of about 4.5. The HBV-associated mechanisms that lead to iCCA are under intense investigation. The diagnosis of iCCA in the context of chronic liver disease is challenging and often requires histological confirmation to distinguish from hepatocellular carcinoma. It is currently unclear whether antiviral treatment for HBV can decrease the incidence of iCCA. In terms of management, surgical resection remains the mainstay of treatment. There is a need for effective treatment modalities beyond resection in both first- and second-line treatment. In this review, we summarize the epidemiological evidence that links the two entities, discuss the pathogenesis of HBV-associated iCCA, and present the available data on the diagnosis and management of this cancer.

**Key Words:** Cholangiocarcinoma; Hepatitis B; Intrahepatic; Hepatocellular carcinoma; Resection; Chemotherapy

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**Core Tip:** Cholangiocarcinoma (CCA) is the second most common primary liver cancer. Intrahepatic CCA (iCCA), a subgroup of CCA, has a pronounced association with hepatitis B virus (HBV) infection. Recent data have strengthened this association

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both in terms of epidemiology and pathogenesis. Moreover, the potential for the development of the combined hepatocellular-cholangiocarcinoma form poses additional difficulties in the successful management of iCCA. Herein, we discuss the available epidemiological data, present the current knowledge on the pathogenesis of HBV-associated iCCA, and review all of the available information on the diagnosis and management of this aggressive cancer.

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## INTRODUCTION

A 61-year-old woman with compensated liver cirrhosis due to chronic hepatitis B (CHB) presented to the outpatient clinic of our hospital for her semi-annual evaluation. She had started antiviral treatment with entecavir (0.5 mg per day) approximately 2 years prior. Her family history is significant for hepatocellular carcinoma (HCC), as her twin brother also suffered from liver cirrhosis due to CHB. On physical examination, no signs of liver decompensation were detected. Her liver synthetic function and alpha fetoprotein (AFP) value were completely normal. However, a small (1.8 cm) liver nodule with arterial enhancement was discovered in the left hepatic lobe during magnetic resonance imaging (MRI) (Figure 1). Hence, the patient underwent left hepatectomy without complications. Surprisingly, histological examination of the surgical specimen revealed a definite intrahepatic cholangiocarcinoma (CCA) (Figure 2).

This case vignette highlights the possible association between hepatitis B virus (HBV) infection and intrahepatic CCA (iCCA). iCCA is a subgroup of CCA that accounts for about 10%-20% of the total cases and classically arises above the second-order bile ducts[1]. iCCA was recently recognized as a distinct entity opposed to the extrahepatic type of CCA (eCCA)[2]. Several predisposing factors that contribute to the development of CCA have been described. A recent meta-analysis clearly showed that the degree to which these risk factors are associated with the development of this cancer significantly differ according to the tumor location[3]. Specifically for HBV infection, the odds ratio (OR) for the development of CCA is much greater for iCCA than for eCCA (4.57 vs 2.11). In view of these findings, several questions regarding this association arise such as how accurately can we distinguish between HCC and iCCA; what are the mechanisms that lead to the formation of iCCA; is there a specific role for HBV in iCCA; and finally, can antiviral treatment against HBV reduce the incidence of iCCA. In this review, we summarize the epidemiological evidence that links the two entities, discuss the pathogenesis of HBV-associated iCCA, and present the available data on the diagnosis and management of this aggressive cancer.

## EPIDEMIOLOGICAL STUDIES OF HBV-ASSOCIATED ICCA

To identify relevant epidemiological studies from geographically diverse regions, a comprehensive literature search of PubMed was conducted up to December 2020 without language restrictions. Studies were eligible for inclusion if they met the following criteria: were case-control or cohort study design, reported outcomes for the association between HBV infection and iCCA, and provided risk estimates with 95% confidence intervals (CIs) or sufficient data to calculate them. The following Medical Subject Headings were included: "intrahepatic cholangiocarcinoma" and "HBV." Reference lists of the retrieved articles were also manually searched to identify additional studies.

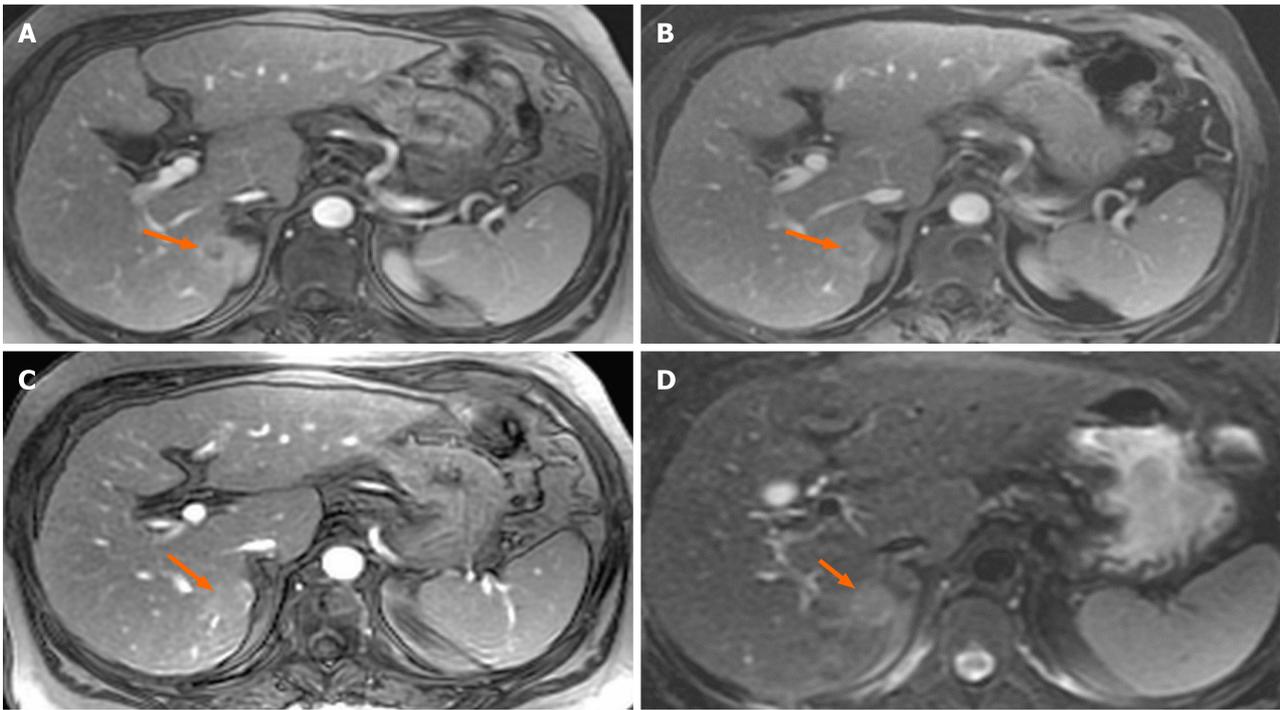
The literature search identified a total of 417 references, of which 20 case-control[4-23] and 2 cohort studies[24,25] fulfilled the inclusion criteria (Table 1). The population of the included epidemiological studies originated not only from geographical regions of high or intermediate prevalence of cholangiocarcinoma (*i.e.* Thailand, South Korea,

**Table 1 Summary of epidemiological studies evaluating hepatitis B virus infection and risk of intrahepatic cholangiocarcinoma**

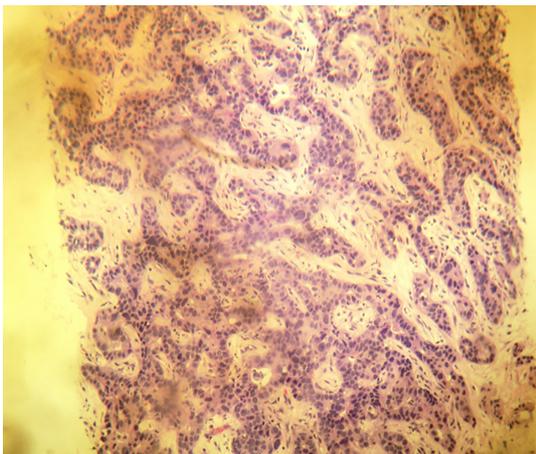
Ref.	Study design	Region	Dates	Source	Age (yr)	Gender (% male)	Cases		Controls		OR (95%CI) for HBV infection
							Total	With exposure (%)	Total	With exposure (%)	
Petrick <i>et al</i> [4], 2017	Case-control	United States	2000-2011	Population	78.0	46.6	2092	25 (1.2)	323615	1200 (0.4%)	2.97 (1.97-4.46)
Choi <i>et al</i> [5], 2016	Case-control	United States	2000-2014	Hospital	60.6	42.9	1169	10 (0.95)	4769	8 (0.2%)	12.9 (2.69-61.61)
Huang <i>et al</i> [6], 2017	Case-control	Taiwan area of China	2003-2009	Population	67.7	52.1	4695	138 (2.9)	46942	513 (1.1%)	2.23 (1.80-2.76)
Lee <i>et al</i> [7], 2015	Case-control	South Korea	2007-2013	Hospital	67.8	50.4	83	19 (22.9)	166	9 (5.4%)	4.58 (2.00-10.50)
Chaiteerakij <i>et al</i> [8], 2013	Case-control	United States	2000-2010	Hospital	61.2	50.3	612	3 (0.5)	594	3 (0.5%)	0.97 (0.20-4.80)
Chang <i>et al</i> [9], 2013	Case-control	China	2004-2008	Population	NR	56.1	2978	257 (8.6)	11912	229 (1.9%)	4.9 (4.1-5.9)
Wu <i>et al</i> [10], 2012	Case-control	China	2002-2008	Hospital	57.9	62.1	23	12 (52.2)	52	2 (3.9%)	38.9 (7.52-201.04)
Wu <i>et al</i> [11], 2012	Case-control	China	1998-2010	Hospital	58.7	55.9	102	28 (22.5)	809	27 (3.3%)	10.52 (5.94-18.62)
Peng <i>et al</i> [12], 2011	Case-control	China	2002-2009	Hospital	53.8	60.2	98	31 (31.6)	196	25 (12.8%)	2.75 (1.27-5.95)
Welzel <i>et al</i> [13], 2011	Case-control	United States	1994-2005	Population	76.4	52.5	743	11 (1.5)	195953	442 (0.2%)	3.07 (1.43-6.58)
Tao <i>et al</i> [14], 2010	Case-control	China	1998-2008	Hospital	58.7	60.7	61	17 (27.9)	380	19 (5.0%)	7.3 (3.1-17.2)
Zhou <i>et al</i> [15], 2010	Case-control	China	2003-2006	Hospital	53.1	70.3	317	154 (48.6)	634	42 (6.6%)	9.67 (6.33-14.77)
Lee <i>et al</i> [16], 2009	Case-control	Taiwan area of China	1991-2005	Hospital	61.5	63.1	160	60 (37.5)	160	22 (13.8%)	4.99 (2.78-8.95)
Lee <i>et al</i> [17], 2008	Case-control	South Korea	2000-2004	Hospital	60.7	69.1	622	84 (13.5)	2488	125 (5.0%)	2.3 (1.6-3.3)
Zhou <i>et al</i> [18], 2008	Case-control	China	2004-2006	Hospital	53.2	66.0	312	151 (48.4)	438	42 (9.6%)	8.88 (5.97-13.19)
Shaib <i>et al</i> [19], 2007	Case-control	United States	1992-2002	Hospital	59.8	55.4	83	1 (1.2)	236	1 (0.4%)	2.9 (0.1-236.8)
Choi <i>et al</i> [20], 2006	Case-control	South Korea	2003-2004	Hospital	64.0	62.2	51	4 (7.8)	51	5 (9.8%)	0.8 (0.19-3.02)
Shaib <i>et al</i> [21], 2005	Case-control	United States	1993-1999	Population	78.7	51.7	625	1 (0.2)	90834	182 (0.2%)	0.8 (0.1-5.9)
Yamamoto <i>et al</i> [22], 2004	Case-control	Japan	1991-2002	Hospital	64.6	58.0	50	2 (4.0)	205	5 (2.5%)	1.84 (0.34-10.11)
Donato <i>et al</i> [23], 2001	Case-control	Italy	1995-2000	Hospital	65.0	80.8	23	3 (13.0)	824	45 (5.5%)	2.7 (0.4-18.5)
Tanaka <i>et al</i> [24], 2010	Cohort	Japan	1991-1993	Population	40-60	54.4	9.08/100000 p-yrs		0.66/100000 p-yrs		8.56 (1.33-55.20)
Fwu <i>et al</i> [25], 2011	Cohort	Taiwan area of China	1983-2000	Population	28.29	0	0.43/100000 p-yrs		0.09/100000 p-yrs		4.80 (1.88-12.20)

Hepatitis B virus infection status was identified by positive serum Hepatitis B surface antigen (HBsAg), unless reported otherwise. Cohort studies reported incidence rates of intrahepatic cholangiocarcinoma per 100000 HBsAg seropositive person-years (p-yrs). CI: Confidence interval; HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus; iCCA: Intrahepatic cholangiocarcinoma; NR: Not reported; OR: Odds ratio.

Japan, Mainland China and Taiwan area of China) but also from regions of low preva



**Figure 1** A small (1.8 cm) liver nodule with arterial enhancement is discovered in the left hepatic lobe during magnetic resonance imaging. A: T1, arterial phase; B: T1 portal phase; C: T1 delayed phase; D: T2.



**Figure 2** Histological findings typical of cholangiocarcinoma.

Twenty case-control studies were included (seven from Mainland China[9-12,14,15, 18], six from the United States[4,5,8,13,19,21], three from South Korea[7,17,20], two from Taiwan area of China[6,16] and one each from Japan[22] and Italy[23]), involving 14899 patients and 681258 cases. Notably, only 4 of the 20 retrieved studies were published in the last 5 years. Population-based controls were employed in 3 studies from the United States[4,13,21] and 1 from Mainland China[9] and the Taiwan area of China[6], whereas the remaining 15 studies were hospital-based. HBV infection status was defined by the presence of hepatitis B surface antigen (HBsAg) in 15 studies[5,7,8, 10-12,14-20,22,23] and by international classification of diseases-9 coding in 5 studies[4, 6,9,13,21]. Seropositivity of hepatitis B core antibody (HBcAb) was assessed in five studies[10-12,14,19]. All of the included case-control studies reported adjustments for age and gender. Fourteen studies showed a statistically significant association between HBV infection and risk of iCCA (range of individual OR = 2.23-12.9)[4-7,9-18], whereas the rest of the studies ( $n = 6$ ) did not[8,19-23]. These six studies were concluded prior to 2002 in geographically different areas. Geographical variations in iCCA incidence may be explained by differences in environmental and genetic risk factors. Moreover,

observational studies are difficult to control for confounders, which could present an important risk factor and influence the prognostic value of HBV infection in iCCA.

Two large-scale cohort studies with a total of 1937215 participants evaluating the correlation between HBV infection and iCCA were identified (Table 1). A retrospective cohort study from Japan involved 154814 blood donors with a median follow-up period of 7.6 years and reported an iCCA incidence rate of 0.88 per 100000 person-years[24]. Compared with individuals negative for both HBsAg and hepatitis C virus antibody (anti-HCV), those who tested positive for HBsAg had a significantly higher risk of iCCA (hazard ratio [HR] = 8.56; 95%CI: 1.33-52.20). The latter study from Taiwan area of China included a cohort of 1782401 pregnant women with a median follow-up of 6.91 years and reported 18 cases of iCCA[25]. Women seropositive for HBsAg had significantly increased incidence rates of iCCA (0.43 per 100000 person-years) than HBsAg-negative women (0.09 per 100000 person-years) with an age-adjusted hazard ratio HR = 4.80; 95%CI: 1.88-12.20.

Occult HBV infection (OBI), which is defined by the detection of HBV DNA in the serum and liver tissue of HBsAg-negative individuals with or without serological markers of previous viral exposure[28], is an emerging risk factor for iCCA. HBV maintains its pro-oncogenic properties in patients with OBI[29]. Indeed, epidemiological and molecular studies have indicated that OBI represents an important risk factor for the development of cirrhosis and HCC[30,31]. Relevant evidence from pathological studies, investigating the presence of HBV DNA, genes, and proteins in iCCA tissue specimens, also suggests a possible etiological role of OBI in iCCA[32-34]. A case-control study of 183 cryptogenic iCCA patients and 549 healthy individuals confirmed that HBsAg seroclearance does not signify eradication of HBV and may not entirely prevent the development of iCCA in Chinese patients[32]. Pollicino *et al*[33] investigated the presence of HBV DNA in liver tissue specimens from 47 HBsAg-negative patients with iCCA and 41 paired non-tumor liver tissues. A high prevalence of OBI in iCCA patients, along with the presence of both free viral genomes and integrated HBV DNA in the tumor tissue, suggested an involvement of HBV in the carcinogenesis of iCCA not only in overt but also in occult infection[33].

To date, there are limited data on the relationship between iCCA and HBV genotype. Barusrux *et al*[35] investigated the prevalence of HBV and HCV infection among 295 CCA patients in northeast Thailand[35]. In this study, HBV genotypes C (73.3%) and B (26.7%) were detected, in line with the HBV genotype distribution in Thailand[36]. In a cohort of 11 cases of iCCA in the eastern United States, liver specimens were examined for HBV DNA and HCV RNA and the genotypes observed represented the dominant genotype (genotype A) in this area[37]. Currently, there is no sufficient evidence to support an etiological association between specific HBV genotypes and iCCA.

### Meta-analyses of HBV-associated iCCA

To address the inconsistent results reported in previous epidemiological studies, an overview of the most comprehensive meta-analyses exploring the association between HBV infection and iCCA is provided (Table 2). A total of six systematic reviews and meta-analyses were retrieved[3,38-42], two of which focused on the risk factors of iCCA alone[41,42]. The remaining studies assessed HBV infection as a sole factor or among other risk factors for both iCCA and eCCA[3,38-40]. Of these, two meta-analyses were published in 2020 (one from the United Kingdom[3] and the other from China[38]), one in 2016 from China[39] and three in 2012 (two from China[40,42] and one from the United States[41]). In four meta-analyses, the population of the primary epidemiological studies originated from both Eastern and Western countries[3,40-42], whereas the remaining two meta-analyses included studies only from Asia[38,39]. The period of data collection among these primary studies ranged from 1987 to 2014.

All of the included meta-analyses suggested that HBV infection was significantly associated with an increased risk of iCCA (range of pooled OR = 3.17-5.98)[3,38-42]. A moderate to severe degree of statistical heterogeneity was noted across the primary epidemiological studies, as assessed by Cochran's Q and  $I^2$  statistic (Table 2). Publication bias was identified in two meta-analyses[38,42].

To the best of our knowledge, the most up-to-date systematic review and meta-analysis were performed by Clements *et al*[3] in 2020. A total of 13 risk factors, including HBV, were evaluated for iCCA and eCCA. Eighteen case-control studies were included to study the association between HBV and iCCA. The pooled risk estimate (OR = 4.57; 95%CI: 3.43-6.09) showed a statistically significant increased risk of iCCA with HBV infection. Furthermore, meta-regression analysis indicated that in Eastern countries, HBV conferred a greater risk of iCCA than in Western countries. Similar geographical differences for the association of HBV with iCCA have been

Table 2 Summary of meta-analyses evaluating hepatitis B virus infection as a risk factor for intrahepatic cholangiocarcinoma

Ref.	Number of included studies	Data collection period	Regions	Cases	Controls	Pooled OR (95%CI) for HBV infection	Heterogeneity	Publication bias
Clements <i>et al</i> [3], 2020	Case-control = 18	1991-2014	Eastern = 12. Western = 6	14825	681181	4.57 (3.43-6.09)	$I^2 = 83\%$ $Q = 100.88$ ( $P < 0.001$ )	Funnel plot: Symmetrical. No bias
Tan <i>et al</i> [38], 2020	Case-control = 6	1998-2013	Eastern = 6	3623	13597	5.98 (4.08-8.76)	$I^2 = 69\%$ $Q = 16.01$ ( $P = 0.07$ )	Funnel plot: Relatively symmetrical. Moderate bias
Zhang <i>et al</i> [39], 2016	Case-control = 11	1991-2013	Eastern = 11	4966	17752	3.18 (2.35-4.30)	$I^2 = 84\%$ $Q: P < 0.001$	Begg's test: $P = 0.75$ , Egger's test: $P = 0.42$ . No bias
Li <i>et al</i> [40], 2012	Case-control = 11. Cohort = 2	1991-2008	Eastern = 10. Western = 3	2402. NA	96266. NA	3.42 (2.46-4.74)	$I^2 = 75\%$ $Q = 48.37$ ( $P < 0.001$ )	Funnel plot: Symmetrical Begg's test: $P = 0.70$ , Egger's test: $P = 0.26$ . No bias
Palmer <i>et al</i> [41], 2012	Case-control = 8	1991-2008	Eastern = 5. Western = 3	2753	291756	5.54 (3.19-9.63)	$I^2 = 86.3\%$ $Q = 51.2$ ( $P < 0.001$ )	Funnel plot: Symmetrical. No bias
Zhou <i>et al</i> [42], 2012	Case-control = 12. Cohort: = 2	1987-2009	Eastern = 11. Western = 3	2362. NA	96452. NA	3.17 (1.88-5.34)	$I^2 = 81\%$ $Q: P < 0.001$	Funnel plot: Asymmetry. Moderate bias

Statistical heterogeneity was assessed by the Cochran's Q statistic and  $I^2$  statistic. Significant heterogeneity is considered if  $Q: P < 0.10$  or  $I^2 > 60\%$ . Publication bias was evaluated using the Begg's funnel plot and Egger's test with  $P < 0.10$  as an indication of publication bias. CI: Confidence interval; HBV: Hepatitis B virus; ICC: Intrahepatic cholangiocarcinoma; NA: Not applicable; OR: Odds ratio.

reported by Li *et al*[40], however Palmer and Patel[41] did not reveal any significant difference between Eastern and Western populations.

## PATHOGENESIS OF HBV-ASSOCIATED ICCA

Cholangiocarcinoma is a multifactorial heterogeneous disease of diverse predisposing factors. However, regardless of underlying etiology, chronic inflammation seems to be a common denominator of most risk factors for CCA as they are usually associated with inflammation or cholestasis. Chronic inflammation leads to increased production of a multitude of inflammatory mediators such as interleukin-6 (IL-6), tumor necrosis factor (TNF), cyclooxygenase-2, and Wnt, resulting in an "activated" environment favoring successive mutations of tumor suppressor genes, and other oncogenes. Other mediators found to be upregulated in CCA include transforming growth factor beta (TGF- $\beta$ ), vascular endothelial growth factor, hepatocyte growth factor, and several microRNAs[43]. Most of those changes promote angiogenesis and cell proliferation.

In particular, liver cirrhosis regardless of etiology represents an inflammatory process that is clearly associated with the development of ICCA. Several population-based studies have confirmed cirrhosis as an important risk factor not only for HCC but also for iCCA[44]. A meta-analysis found that cirrhosis causes iCCA with an OR as high as 22[41]. Furthermore, a retrospective analysis of United States-based Surveillance, Epidemiology, and End Results found that cirrhosis is associated with both iCCA (OR 8.26) and eCCA (OR 3.83)[4]. As chronic infection with HBV and HCV account for most cases of cirrhosis globally, it is not surprising that a definite association between viral hepatitis infection and iCCA has been observed. A large meta-analysis produced an OR for iCCA of 3.17 and 3.42 for HBV and HCV, respectively [42]. A distinct phenotype of viral hepatitis-related iCCA that more frequently affects younger males and is characterized by mass-forming tumors with cholangiolar differentiation, higher aFP, lower carbohydrate antigen (CA) 19-9 levels and higher N-cadherin expression has been suggested[12,45,46]. Such tumors are more commonly associated with cirrhosis or elevated prothrombin time. Recent studies have suggested that HBV-associated iCCA displays infrequent nodal metastases and confers better a prognosis, whereas patients with CCA associated with HCV may fare worse[47,48]. In addition, viral hepatitis-associated CCA more frequently expresses programmed death-ligand 1 (PD-L1), which in theory may be exploited for the development of immunotherapy strategies[49].

Inflammation is a multifactorial and diffuse process. It involves multiple pathways acting through diverse mechanisms in an environment conducive of proliferation and oncogene mutations leading to malignant transformation. As a result, there has been no single molecular alteration characteristic of CCA. IL-6, a strong proinflammatory cytokine has a pleiotropic role, by increasing cell proliferation through activation of the Janus kinase-signal transducer and activator of transcription pathway; it also promotes expression of antiapoptotic myeloid leukemia cell differentiation protein and the activation of both the Akt and mitogen-activated protein kinase kinase (MEK)-extracellular signal-related kinase (ERK) pathways, which results in strong proliferative and anti-apoptotic effects[50-52]. In such an activated environment, increased DNA instability may lead to critical genetic alterations of the excited cells, and also increases the probability of mutations of important genes such as tumor suppressor gene p53 and the MYC proto-oncogene, among others[53]. The DNA instability is at least partially attributable to the effect of TNF- $\alpha$ , which among others, causes the upregulation of activation-induced cytidine deaminase, an enzyme that can create DNA mutations by converting cytosine to uracil.

In addition to the inflammatory changes caused in the liver tissues by the continuous presence of the virus, it seems that hepatitis viral components may act as oncogenes and promote oncogenicity *per se*. In particular, hepatitis B x (HBx) protein has been implicated in carcinogenesis. Experiments with transgenic mice have demonstrated that its expression enhances IL-6-dependent proinflammatory effects and causes malignant transformation towards both HCC and CCA[54].

The presence of HBV genes in the genome of CCA has been described. Although the exact effect on tumorigenesis is unknown, the observed proximity of the insertion sites to the gene encoding the tumor suppression p53 is intriguing. Wang *et al*[55] using *in situ* hybridization demonstrated the presence of HBV genes in 33 of 40 iCCA cases tested; the most common gene found was again HBx[55]. In a study by Pollicino *et al* [33] employing a PCR technique, incorporation of HBV genes in patients with iCCA and no overt viral infection was detected in tumor or non-tumorous liver cells in 29 of the 47 examined cases, suggesting the importance of occult viral infection in the development of CCA. Most cases involved the HBx gene.

Expression of the culprit HBx gene may be documented by immunohistochemistry in about 70% of patients with iCCA and correlates with peripheral tumors and higher aFP levels, but the exact percentage obviously depends on the epidemiology of the tested population[56]. Co-expression of HBx and HCV core proteins in transgenic zebra fish livers induces fibrosis and iCCA[57], and is associated with activation of the phosphorylated Smad3L oncogenic pathway with consequent phosphorylation and activation of MEK-ERK proteins. Bile duct proliferation, fibrosis, and iCCA were markedly reduced by knockdown of TGF- $\beta$ , suggesting the important role of this mediator. Semaphorine 3B is a recently identified tumor suppressor gene encoded on chromosome 3p21.3 and is connected to p53 activity. Silencing of the locus due to gene or promoter hypermethylation or loss of homozygosity was detected in several CCA tumor cells, and as expected, was associated with the downregulation of mRNA transcripts[43].

These dysregulations result in a broad variety of somatic mutations that have been recently identified using next-generation sequencing, some of which impair the function of known oncogenes. Almost any gene implicated in carcinogenesis is abnormal in CCA, attesting to the heterogeneity of the disease and the lack of a pathognomonic driver mutation[58]. Thus, KRAS mutations may affect 20% of CCA. Mutations of isocitrate dehydrogenase 1 (IDH1) and IDH2 genes occur in approximate 20% of iCCA. IDH1 and IDH2 genes encode for enzymes active in the citric acid cycle (Krebs cycle), and their loss of function mutations results in accumulation of an abnormal oncometabolite R-2-hydroxyglutarate which interferes with the function of several pathways and causes epigenetic DNA changes. Other alterations of iCCA include fibroblast growth factor receptor 2 (FGFR2) mutations. Translocation or amplification of the FGFR2 locus is found in 19% of 122 iCCA patients[59]. Tumors of such patients tend to be of the mass-forming type and compared to non-FGFR2 altered tumors, they secrete less mucus and are more commonly associated with HBV infection.

Although some of these alterations appear to be important for the malignant behavior of the tumor, they may not represent the initiating transforming event, which should be sought earlier in the pathogenesis of iCCA. There is enough evidence to suspect that chronic, overt or occult, infection with hepatitis virus may trigger the transformation of infected cells in the context of a conducive, inflammatory environment. Of the various HBV genes, evidence suggests that HBx plays the most crucial role. HBx protein promotes cell cycle progression, inactivates negative growth

regulators, and binds to and inhibits expression of the p53 tumor suppressor gene, other tumor suppressor genes, and senescence-related factors[60]. It appears that some of these actions are mediated through overexpression of telomerase (hTERT) mainly by interfering with its promoter. Thus, the importance of HBx was demonstrated in an experiment involving HCC cell lines, whereby transfection with HBx resulted in the overexpression of hTERT a factor important for the non-senescence of transformed cells[61]. Using current sequencing technology, it appears that the integration of viral sequences to human DNA tends to aggregate in the vicinity of the telomerase gene, although other sites of viral gene insertion of unclear significance have been observed [62]. Interestingly, HBV gene insertions (hepatitis B S and/or C gene fragments) have also been noted in the normal hepatocytes of patients, albeit at reduced frequency. The capacity of HBx gene insertion to directly promote the expression of TERT was demonstrated in a direct transfection experiment in CCA cell lines; HBx gene resulted in cis-activation of TERT mRNA transcription[46]. **Figure 3** summarizes the potential pathological mechanisms that lead to carcinogenesis in patients with hepatitis B.

It can be concluded that mounting evidence supports the theory that chronic, overt, or latent infection with HBV has direct causative effects on the development not only of HCC but also of iCCA, perhaps by acting on a common progenitor cell. The effect of certain viral genes, such as HBx, seems to have direct oncogenic capacity beyond the genetic instability produced by the chronic inflammation, perhaps aided by the latter. These observations support the epidemiologic data linking CHB to the development of iCCA and call for further studies to fully reveal the intricate interaction of the virus with the cellular mechanisms leading to carcinogenesis.

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## CLINICAL PRESENTATION

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Patients with iCCA usually present with unspecific symptoms such as abdominal pain, malaise, night sweats, and cachexia[63]. Jaundice is usually a sign of advanced disease. In particular, patients with HBV-associated iCCA can be diagnosed before they develop any symptoms, due to the fact that they undergo annual or semi-annual surveillance for HCC, which enables iCCA diagnosis at a relatively early stage[64].

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## DIAGNOSIS

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### *Imaging techniques*

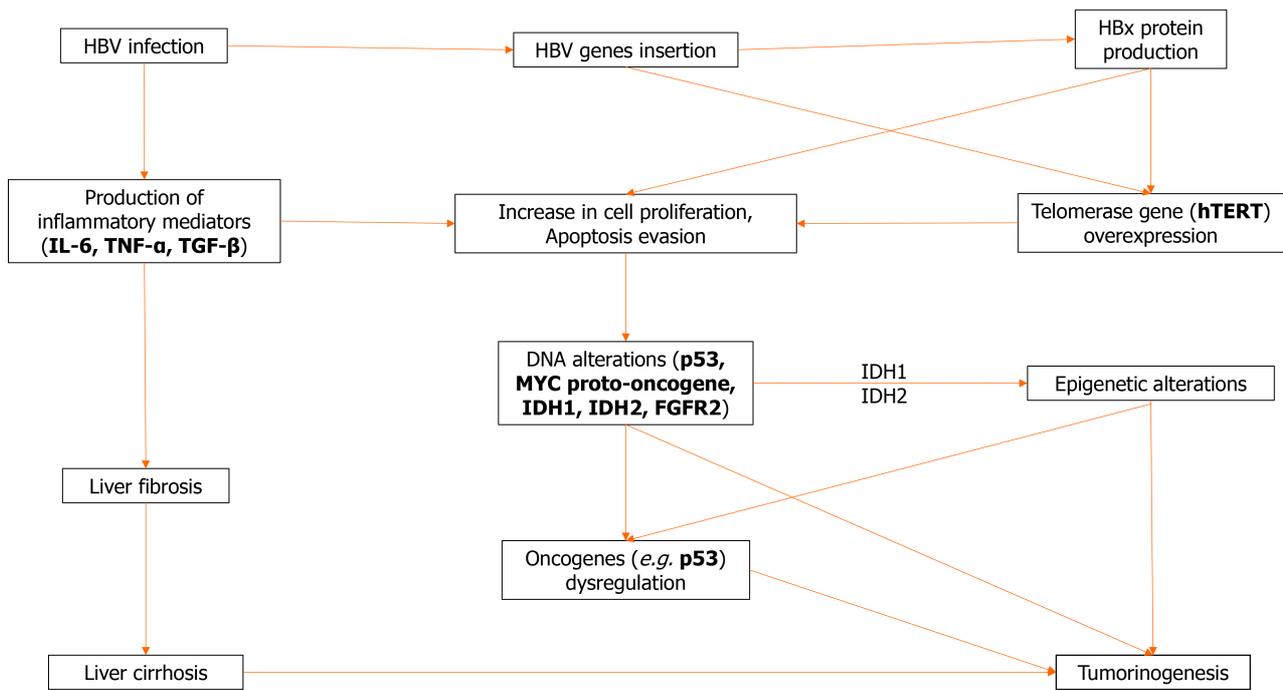
Imaging modalities, such as computed tomography (CT), MRI, and fluorodeoxyglucose positron emission tomography (FDG-PET) can be of great value in the management of iCCA in terms not only of diagnosis but also of staging, follow-up, and assessment of treatment response.

CT scan serves as the standard imaging method for the preoperative assessment of iCCA. It provides a comprehensive evaluation of the primary tumor, the relationship between the primary tumor and adjacent structures such as the hepatic artery or portal vein, and the whole abdomen surveillance for potential metastases[65]. On both contrast-enhanced CT and MRI scans, iCCA usually presents as a mass with irregular borders, peripheral rim enhancement on the arterial phase with progressive homogeneous contrast agent uptake until the delayed or stable uptake during late dynamic phases[66,67]. However, smaller tumors are less likely to demonstrate these characteristics and may be hard to distinguish from HCC, especially in the context of chronic liver diseases.

The utility of FDG-PET for iCCA diagnosis and management is still controversial. Although mass-forming iCCA can be detected with a reported sensitivity of 85% to 95%, it cannot be used for the diagnosis of iCCA as it is not specific enough[68]. However, it could prove useful in detecting distal, unexpected metastases. In fact, a recent meta-analysis suggested that it can bring changes to the management of a substantial portion of iCCA patients[69]. Therefore, it could be considered an option prior to surgical resection (SR) to rule out distant metastatic foci.

### *Serum markers*

Tumor markers in serum are not specific for iCCA, but may be of diagnostic value in some cases. Widely used tumor markers such as CA 19-9 and carcinoembryonic antigen have significant overlap with other cholestatic diseases and low sensitivity for early stage disease, consequently limiting their use[70]. However, high values of these



**Figure 3 Pathological mechanisms that lead to tumorigenesis in patients with hepatitis B virus infection.** FGFR: Fibroblast growth factor receptor; HBV: Hepatitis B virus; IDH: Isocitrate dehydrogenase; IL-6: Interleukin 6; TGF-β: Transforming growth factor β; TNF-α: Tumor necrosis factor α.

markers have been connected with a deterioration in overall survival (OS)[71,72]. As a result, high (> 500 ng/mL) levels of CA 19-9 in the absence of jaundice are considered a relative contraindication for resection of iCCA[73].

However, in cases of HBV-associated iCCA, these markers tend to be even less sensitive[48]. Instead, it has been suggested that such patients tend to have higher levels of aFP, a serum marker widely used for HCC diagnosis, probably because of the fact that both malignancies originate from hepatic progenitor cells, which have the ability to produce aFP[16,46,74,75].

### Histological diagnosis

Pathological diagnosis is recommended for all patients who will undergo systemic chemotherapy or radiation therapy, or take part in a therapeutic clinical trial[68,76]. It should be noted that although a positive result demonstrates the presence of the tumor, a negative result does not exclude it because of the potential sampling errors. In such cases, repeat sampling is often required to confirm the correct diagnosis[77].

According to the World Health Organization (WHO) classification for biliary tract cancer[78], iCCA can be further classified to two main subtypes according to the level or size of the affected duct; large duct type, which resembles eCCA and small duct type, which shares etiological, pathogenetic, and imaging characteristics with HCC and usually develops on a background of chronic liver disease (such as chronic viral hepatitis and cirrhosis)[58]. Small bile duct iCCA presents as a tubular or acinar adenocarcinoma with nodular growth invading the liver parenchyma, and with no or minimal mucin production[79-81]. Characteristic findings of small bile duct iCCA are IDH1 and IDH2 mutations or FGFR2 fusions or translocations[80-82]. In HBV-associated iCCA, there are data indicating the presence of hyperactivated programmed cell death protein 1/PD-L1 signaling and increased expression of N-cadherin and HBx protein[45,49,56]. It remains to be seen if these diagnostic characteristics can also serve as potential therapeutic targets.

### Staging

iCCA is mainly staged according to the 8<sup>th</sup> edition of the American Joint Committee on Cancer (AJCC) TNM system (Tables 3 and 4). Despite providing some meaningful contribution to the patient's prognostication, it does have some rather important limitations. First, although the tumor size was introduced for the first time in the latest AJCC Cancer Staging Manual, the only discriminating size cut-off used is the one of < 5 cm encompassing all T1 tumors. However, there are some data indicating that patients with very small (< 2 cm) tumors have potentially better outcomes in terms of

**Table 3 American Joint Committee on Cancer staging classification for intrahepatic cholangiocarcinoma (8<sup>th</sup> edition, 2017)**

Staging classification	
T1a	Solitary tumor ≤ 5 cm without vascular invasion
T1b	Solitary tumor > 5 cm without vascular invasion
T2	Solitary tumor with vascular invasion, or multiple tumors with or without vascular invasion
T3	Tumor perforating the visceral peritoneum
T4	Tumor involving the local extrahepatic structures by direct invasion
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis present
M0	No distant metastasis
M1	Distant metastasis present

**Table 4 American Joint Committee on Cancer staging classification for intrahepatic cholangiocarcinoma (8<sup>th</sup> edition, 2017)**

Stage	T	N	M
Ia	T1a	N0	M0
Ib	T1b	N0	M0
II	T2	N0	M0
IIIa	T3	N0	M0
IIIb	T4	N0	M0
	Any T	N1	M0
IV	Any T	Any N	M1

survival, rendering them eligible for different therapeutic modalities[83]. In addition, the latest TNM system fails to include parameters such as performance status (PS) or the severity of liver function impairment. Both of these limitations are clearly extremely important for assessing the prognosis of patients with HBV-associated iCCA, as very small tumors can be detected during surveillance programs and may also have advanced parenchymal liver disease.

## THE CASE OF COMBINED HCC AND CHOLANGIOCARCINOMA

Combined HCC-CCA (cHCC-CCA) is a rare type of primary liver cancer (PLC), which has been defined as a distinct carcinoma displaying features of both hepatocytic and cholangiocytic differentiation[84]. Since the first description of this entity in 1949[85], significant terminology changes have been introduced. The 2010 WHO classification system distinguishes a classical form of cHCC-CCA and three variants with stem/progenitor cell features including typical, intermediate cell, and cholangiolocellular subtypes[86]. However, molecular advancements throughout the years have challenged the validity of stemness; thus, the term “typical subtype” has been abandoned; cholangiolocellular carcinoma is currently considered to be a subtype of iCCA, but it can still be within the spectrum of cHCC-CCA only if an HCC component is also involved and is currently addressed as “cholangiolocarcinoma”; PLCs consisting exclusively of intermediate cells are specified as intermediate cell carcinomas, while the role of intermediate cells in cHCC-CCA is still debated[84,87,88].

Large series have reported that cHCC-CCA represents 0.77%-5.8% of all PLCs[89, 90]. Viral hepatitis (HBV, HCV), alcohol abuse, and cirrhosis have been associated with this cancer. Notably, cirrhosis and HBV infection are more commonly related with cHCC-CCA than iCCA, although with lower rates compared to HCC[91-94]. Most patients are aged between 50 and 60 years, with comparative studies claiming presentation in a younger age than iCCA[91,95], while others have not managed to point out significant age differences[92,93]. Male predominance is well documented

(65%-80%)[89,90,95,96] and tends to be more notable opposed to iCCA patients[92]. Studies focusing on HBV-related cHCC-CCA present an even greater male to female ratio that reaches 9:1[97,98].

Imaging features may resemble patterns of HCC, CCA, or both, therefore rendering radiological modalities insufficient to ensure definite diagnosis. Arterial phase hyperenhancement and portal/delayed phase hypoenhancement (washout) are characteristic findings of HCC in CT, MRI, and contrast-enhanced ultrasound; however, they could also be displayed by cHCC-CCA lesions and lead to misdiagnosis [93,99]. Similarly, cHCC-CCA tumors can mimic CCA by displaying gradual enhancement and peripheral irregular rim-like contour. According to Wang *et al*[92], in the former case the presence of lymphadenopathy, elevation of CA 19-9 and/or biliary dilation are in favor of cHCC-CCA, whereas the presence of pseudocapsule and well-defined margin are more suggestive of HCC. In the latter case when cHCC-CCA resembles features of CCA, the presence of simultaneous cirrhosis, HBsAg positivity, pseudocapsule and/or portal vein thrombosis should raise suspicion of cHCC-CCA. Furthermore, concurrent elevation of both aFP and CA 19-9 or discordance between tumor markers and imaging features (*i.e.* radiological hallmarks of HCC accompanied by increased CA 19-9 or lesions resembling CCA with raised aFP) should prompt consideration of cHCC-CCA diagnosis[100,101]. Histopathological examination of biopsies or surgical specimens based on routine stains ultimately establishes the correct diagnosis. Immunohistochemical markers can provide additional information, but are of secondary importance[84].

Complete excision with negative margins and sufficient residual liver volume is the goal of treatment[102]. In a large series of 390 HBV-related cHCC-CCA, the median OS after SR was 20 mo and negative prognostic factors included male gender, number of tumors  $\geq 2$ , major thrombus, gamma-glutamyl transferase (GGT)  $> 60$  IU/L, and CA 19-9 levels[98]. In a recent systematic review, data analyses of 14 studies showed that patients with cHCC-CCA, HCC, and CCA undergoing SR had 5-year survival rates of 32.7%, 47.5%, and 30.3% respectively[96]. Similar outcomes have been published about liver transplantation (LT): HCC patients achieve considerably greater survival rates than cHCC-CCA and CCA subgroups[95,103]. The role of locoregional treatment and systematic chemotherapy in the management of cHCC-CCA remains uncertain. A retrospective analysis of 50 patients with unresectable cHCC-CCA undergoing transarterial chemoembolization (TACE) demonstrated that better response rates could be attained when careful selection is applied (*i.e.* hypovascular tumors respond poorly due to inability of chemotherapeutic agents to reach target)[94]. Limited data about chemotherapy are available; however, it is noteworthy to mention the results of two recent multicenter studies using platinum-based regimens, which were associated with favorable outcomes compared to sorafenib monotherapy[104] and could be potentially effective when used together with gemcitabine as first-line treatment for advanced, unresectable cHCC-CCA[105].

## TREATMENT OF ICCA

### SR

SR is the treatment of choice for all iCCA patients, since it is the only established therapy capable of achieving a possible cure[68,76]. Conventional surgical aim of a SR should be complete tumor resection with negative microscopic (R0) margins while preserving adequate liver volume to avoid post-operative liver failure[73].

The eligibility of a patient for curative surgery should always be determined by a multidisciplinary board on a case-by-case basis. Given the poor prognosis of patients who have multifocal disease or clinically evident lymph node metastasis, SR should be precluded for these patients[106,107]. Regarding macroscopic vascular invasion, although it should generally be considered a contraindication, there are some data from specialized centers supporting that major vascular resection is not associated with worse perioperative or oncologic outcomes[108]. Obviously, as with HCC[109], liver function should be assessed in patients with underlying liver cirrhosis. Restrictions for resection are recommended in cases where liver function is significantly impaired and/or the patient's PS is poor.

As aforementioned, patients with HBV-associated iCCA are often diagnosed at a relatively early stage. This is probably the reason why the proportion of iCCA patients who undergo curative resection is significantly higher for HBV-positive than HBV-negative patients[110]. HBV infection has been identified by many studies as an independent factor associated with favorable outcomes, suggesting that better

prognosis of HBV associated iCCA may be perhaps explained by less aggressive biological nature[111-115]. In fact, a meta-analysis showed that lymph node metastasis occurred less commonly in HBV-associated iCCA than iCCA of other etiology (OR = 0.39)[48]. In a large single-center retrospective study from China that included 1333 iCCA patients (608 HBsAg-positive and 725 HBsAg-negative) the median post-operative survival was 19 mo for HBsAg(+) compared to 12 mo for HBsAg(-) patients ( $P < 0.001$ )[116]. Factors that have been associated with better outcomes for patients with HBV-associated iCCA include tumor diameter  $< 5$  cm, better tumor differentiation, lower serum levels of aFP or CA 19-9 and absence of vascular invasion, lymph node metastasis, extrahepatic metastasis or TP53 mutation[113,117,118].

### Adjuvant chemotherapy

Until a few years ago, the role of adjuvant chemotherapy in the setting of iCCA was not well defined because of a complete lack of data from randomized trials. However, a meta-analysis of retrospective cohorts indicated that administration of chemotherapy in the adjuvant setting provides a survival benefit to patients with iCCA[119]. This contrasted with the randomized PRODIGE 12[120] trial (gemcitabine and oxaliplatin [GEMOX] *vs* surveillance for patients with resected biliary tract cancer) which failed to produce statistically significant results. On the other hand, the BILCAP trial (capecitabine *vs* observation for patients with resected biliary tract cancer)[121], showed a benefit in terms of recurrence-free survival in the intention-to-treat analysis (HR = 0.75,  $P < 0.05$ ) and also in terms of OS in the pre-planned sensitivity analysis (HR = 0.75,  $P < 0.05$ ), both in the first 24 mo from randomization. However, no statistically significant benefit was observed in the intention-to-treat OS analysis of the whole population or the iCCA subgroup. Based on these partial benefits, the American Society of Clinical Oncology published a new guideline recommending that all patients undergoing SR of any biliary tract tumors should be offered adjuvant capecitabine chemotherapy for 6 mo[122]. More information is expected in the foreseeable future from the ACTICCA-1 study (NCT02170090), a phase III trial investigating the clinical performance of the GEMOX combination compared to capecitabine in the adjuvant setting.

### Antiviral treatment

There are not much data concerning the role of antiviral treatment in the management of HBV-associated iCCA. However, one retrospective study demonstrated that antiviral treatment, even when initiated post-operatively, can provide a significant benefit to the patients compared to patients with high ( $> 2000$  IU/mL) HBV-DNA levels who are left untreated (5-year recurrence rate 70.5% *vs* 86.5%,  $P < 0.001$  and 5-year OS rate 43% *vs* 20.5%,  $P < 0.001$  respectively)[123].

In 2017, a large-scale retrospective study from Taiwan area of China that was based on data from the National Health Insurance Research Database showed that treatment with nucleos(t)ide analogues (NA) is an independent factor for the development of HBV-associated iCCA (HR 0.44,  $P = 0.004$ )[124]. In the population treated with NA, the 5-year cumulative incidence of iCCA was lower compared to the NA-untreated group (0.17% *vs* 0.39%,  $P = 0.005$ ), stating that treatment with NA could contribute in preventing HBV-associated iCCA, in a similar way as it contributes to reducing the risk of HBV-associated HCC.

### LT

LT for iCCA is still a controversial issue. In the era of organ shortage, iCCA was traditionally considered a contraindication for LT, as both the OS and disease-free survival were disappointing. It should be noted that most of this information came from small, retrospective studies with much heterogeneity in transplant protocols. In certain studies, the 5-year OS rate ranged between 30% to 60%[125-128].

Studies focusing on favorable groups of patients who could potentially derive significant benefit from LT have been reported. In a multicenter retrospective study from Spain[129], a subgroup of patients ( $n = 8$ ) with “very early” iCCA (single tumor,  $< 2$  cm) was highlighted. The 5-year OS in this subgroup was 73% compared to 35% for the patients with single tumors  $> 2$  cm or multinodular tumors ( $n = 21$ ). Another international, multicenter study showed similar results, as the actuarial survival rate for “very early” iCCA was 65%[83]. A recent meta-analysis confirmed the results of such efforts (5-year pooled OS rate 71% *vs* 48% for advanced iCCA), stating that a solitary  $< 2$  cm iCCA in a background of cirrhosis should not preclude consideration of LT[130]. It should be noted though, that the application of LT for cirrhotic patients, with “very early” iCCA unresectable due to impaired liver function still requires

validation by a prospective study. Such a study (NCT02878473) is currently recruiting patients and is expected to provide primary results by 2026.

Another interesting subgroup of iCCA patients, who could substantially benefit from LT, are those with locally advanced, unresectable (due to tumor size, location, or multifocality) disease with a durable response or stability after neoadjuvant chemotherapy[131]. In fact, in an interim analysis of a small series of patients ( $n = 6$ ), with large, unresectable iCCA subjected to LT after an at least 6-mo disease stability under neoadjuvant chemotherapy with gemcitabine-based regimens, the 5-year survival was 83%, although, of note, 5-year recurrence rate was 50% [132].

In light of this information, a recent consensus approved by the International Liver Transplant Society recommends that patients with “very early” iCCA may benefit from upfront LT, whereas those with advanced, unresectable iCCA in a non-cirrhotic state may become LT candidates if the disease remains stable after neoadjuvant therapy[133].

## MANAGEMENT OF UNRESECTABLE DISEASE

Unfortunately, many patients with iCCA present with advanced disease that is not amenable to surgery. When assessing a patient with unresectable iCCA, the medical team managing his care should first take into consideration the patient’s PS, as determined by the Eastern Cooperative Oncology Group PS (ECOG-PS) scale. Patients with ECOG-PS  $> 2$  are unlikely to benefit from any treatment and should be managed with best supportive care. After that, the stage of the disease and the molecular profile of the tumor should be assessed in order to decide the most suitable therapeutic approach for each patient.

### Systemic chemotherapy

Systemic chemotherapy is generally recommended for patients with ECOG-PS 0-1 [68]. The combination of gemcitabine and cisplatin (GEMCIS) is used as the first-line therapeutic regimen in patients with advanced iCCA [105,134]. In the ABC-02 trial ( $n = 410$ , all biliary tract cancers) the researchers observed a statistically significant difference in OS and in progression-free survival (11.7 mo *vs* 8.1 mo and 8 mo *vs* 5 mo, respectively) in favor of the GEMCIS combination compared to gemcitabine alone. The GEMOX combination may be used instead in patients with renal function impairment [76]. Additional combinations of chemotherapeutic agents are being investigated in the first-line setting, including more intensive, triple chemotherapy combinations like GEMCIS with nab-paclitaxel [135]. Acelarin is a NA which can achieve greater intracellular concentrations than gemcitabine and its efficacy in combination with cisplatin is currently being investigated in a phase III study as opposed to GEMCIS (NCT04163900).

After disease progression under first-line chemotherapy with GEMCIS, the next best choice is probably the combination of folinic acid, fluorouracil and oxaliplatin (FOLFOX). In the phase III ABC-06 trial, 162 patients who had already signs of disease progression under GEMCIS administration, were randomly assigned to active symptom control alone or concomitant FOLFOX [136]. In this study, differences in 6- and 12-mo survival (35% *vs* 50.6% and 11.4% *vs* 25.9%, respectively) were considered clinically important, although there was no significant difference in the median OS between the two arms (5.3 mo *vs* 6.2 mo).

A recent multicenter study used clinical and pathological data in addition to information from RNA sequencing in order to identify distinct subtypes of iCCA that might have favorable response to specific treatments. In the subtype that was associated with hepatitis B and C, an *in vivo* sensitivity to gemcitabine was observed. This was attributed to a higher expression of gemcitabine-response genes (SLC28A1 and SLC29A1) [137]. However, these findings should be confirmed in large clinical studies prior to establishing a recommendation for patients with hepatitis B.

### Locoregional treatments

Locoregional therapies have implicit appeal as a treatment option for iCCA, as it is a PLC and often the disease burden is either completely or largely confined to the liver [138]. The most widely used types of locoregional therapeutic regimens in iCCA are TACE, radiofrequency ablation (RFA) and microwave ablation (MWA) and transarterial radioembolization (TARE) with Yttrium<sup>90</sup> (Y-90). The possible role of these modalities in the management of iCCA has mainly been investigated by retrospective studies in various settings. Consequently, the results of the studies are difficult to

interpret, due to the high heterogeneity in terms of patient population (chemotherapy naïve or not) and type of treatment.

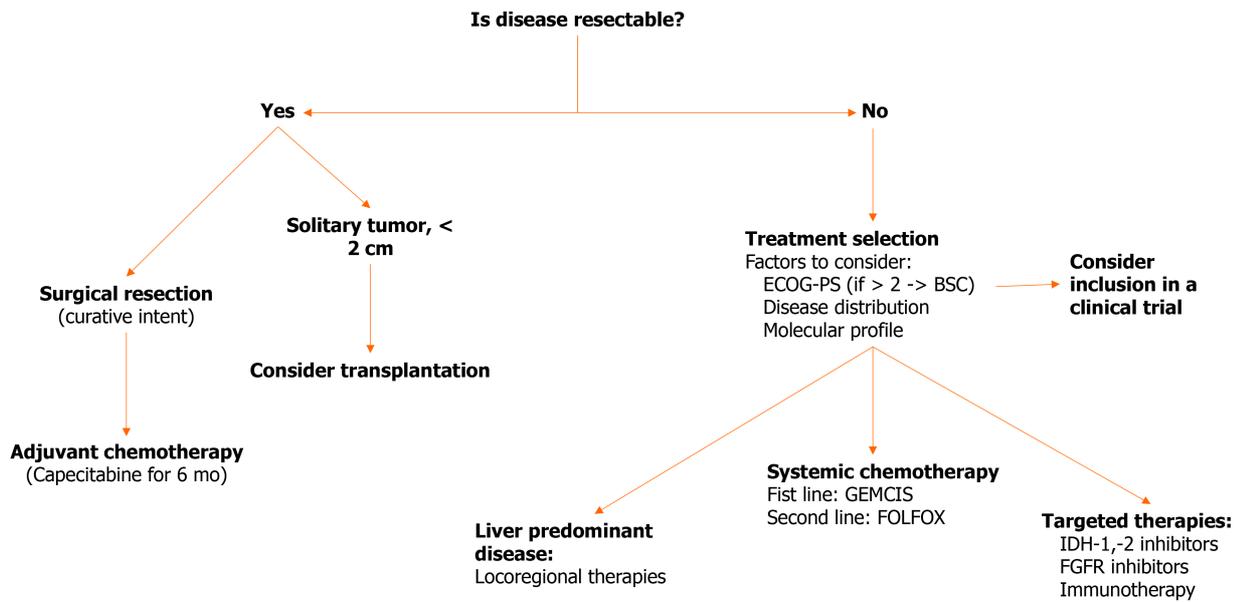
TACE is the most widely used treatment modality for patients with intermediate stage HCC not eligible for curative treatments. The rationale for TACE is based on the hypervascular nature of HCC that enables both strong cytotoxic and ischemic effects following the intra-arterial infusion of a cytotoxic agent and the selective embolization of the blood vessels feeding the tumor. However, iCCA rarely appears hypervascular on CT or MRI studies[68]. Despite that, a retrospective study showed that TACE ( $n = 72$ ) could be beneficial in terms of OS to patients with unresectable iCCA when compared to supportive care ( $n = 83$ , OS = 12.2 vs 3.3 mo, respectively)[139]. However, in another multiinstitutional retrospective study of 188 patients with advanced-stage iCCA, TACE did not seem to have any significant benefit when compared to other arterial-based therapeutic interventions[138]. The efficacy of TACE has also been investigated in the adjuvant setting by a prospective study of 553 consecutive patients (122 TACE vs 431 non-TACE)[140]. Although in the whole cohort, the 5-year OS rates between groups were significantly different (38.4% vs 29.7) after 1:1 propensity score matching no significant differences were observed regarding OS or 5-year recurrence rate. Nevertheless, a recent systematic review and meta-analysis concluded that TACE in the adjuvant setting can actually prolong both the OS and the relapse-free survival [141]. A small, prospective study from China included 42 either HBsAg(+) or HBcAb(+) patients with iCCA who had received SR with curative intent and evaluated the prognostic impact of postoperative TACE[118]. TACE was performed in 9 patients who had demonstrated early recurrence of the tumor within 12 mo from the surgery. The OS of the patients in the TACE ( $n = 9$ ) group was significantly prolonged (1-year, 88.9%; 3-year, 77.8%; 5-year, 66.7%) as compared to the non-TACE ( $n = 33$ ) group (1-year, 63.6%; 3-year, 30.8%; 5-year, 13%), implying that TACE could have a role in the management of patients with HBV-associated iCCA when performed in the adjuvant setting.

A theoretical advantage of ablative therapies like RFA and MWA when compared to TACE, is that they are safe and effective for the local control of hepatic malignancies in patients considered unsuitable for SR without regard to the tumor's vascular profile [142,143]. The efficacy of ablative therapies in the management of unresectable iCCA has been mostly studied in small-scale, retrospective studies. RFA and MWA seem to be helpful for smaller tumors (< 3 cm), but lose part of their effectiveness when it comes to bigger or irregularly shaped tumors resulting in higher recurrence rates[144, 145]. This issue may be overcome by using stereotactic RFA, which combines pre-interventional three-dimensional imaging, computerized three-dimensional planning of electrode positions, and guided electrode placement at arbitrary angulations and orientations[146,147]. In a systematic review and meta-analysis regarding the efficacy of ablative therapies in the management of unresectable iCCA the pooled 1-, 3-, and 5-year OS rates were 76%, 33% and 16%, respectively[148]. It should be noted though, that this systematic review analyzed studies that included cases with various disease stages, such as recurrent or inoperable disease, thus resulting in a high degree of heterogeneity. To our knowledge, there are no published studies regarding the use of ablative therapies in the context of HBV-associated iCCA. It is obvious that in order to extract safer conclusions regarding the role of ablative therapies in the management of iCCA and HBV-associated iCCA in particular, well-designed prospective studies are needed.

In a systematic review and pooled analysis assessing the efficacy of Y-90 in the management of unresectable iCCA, the median OS was 15.5 mo, but the study highlighted the need for prospective studies on this subject[149]. In the MISPEHC study, a phase II single-arm trial where 41 patients were treated with Y-90 and GEMCIS, the results were rather promising, as median OS was 22 mo and 9 patients (22%) were even downstaged to surgery[150]. A phase III randomized trial investigating the efficacy of Y-90 with GEMCIS compared to GEMCIS alone is currently ongoing (NCT02807181). Unfortunately, there are no published studies regarding the use of TARE in the treatment of HBV-associated iCCA.

### Genome-targeted therapies

As our knowledge broadens regarding the DNA alterations and the molecular pathways that are involved in the pathogenesis of HBV-associated iCCA, more possible therapeutic targets are going to arise, until we reach a point where the treatment of each patient will be personalized. As mentioned earlier, some of the most common findings in the genome of viral hepatitis-associated iCCA, include IDH1, IDH2 and FGFR2 mutations. The efficacy of ivosidenib, a targeted inhibitor of IDH1 and IDH2, was investigated in the phase III ClarIDHy trial involving 185 patients with



**Figure 4** Therapeutic algorithm for hepatitis B virus-associated intrahepatic cholangiocarcinoma. BSC: Best supportive care; ECOG-PS: Eastern Cooperative Oncology Group-Performance Status; FGFR: Fibroblast growth factor receptor; FOLFOX: Folinic acid, Fluorouracil and Oxaliplatin combination; GEMCIS: Gemcitabine and cisplatin combination; IDH: Isocitrate dehydrogenase.

chemotherapy-refractory, IDH1 mutant CCA who were randomly assigned to ivosidenib or placebo[151]. The study managed to prove the clinical benefit of targeting IDH1 mutations in such tumors, as progression-free survival was significantly improved, compared to the placebo arm (HR = 0.37,  $P < 0.0001$ ). Inhibitors of FGFR have been tested mostly in smaller, open-label, phase II trials showing some promising results in the treatment of chemotherapy refractory CCA with FGFR alterations[152-154]. In April 2020, the U.S. Food and Drug Administration approved pemigatinib, an FGFR inhibitor for the treatment of adults with previously treated, unresectable locally advanced or metastatic CCA with FGFR2 fusion or other rearrangement. Some additional FGFR inhibitors are currently being evaluated in the first-line setting, such as pemigatinib in the FIGHT-302 study (NCT03656536) and BGJ398 (oral infigratinib) in the PROOF study (NCT03773302).

### Immunotherapy

The clinical data regarding immunotherapy in the management of CCA are limited. Although there is a lot of merit to the idea of a therapeutic approach that targets the immune checkpoint hyperactivation, which is common especially in HBV-associated iCCA, to date, the results from clinical trials are not promising. Pembrolizumab monotherapy provided antitumor activity in just 6% of patients with advanced biliary cancer enrolled in the KEYNOTE-158 study, with median progression-free survival of 2 mo[155]. Possibly, these therapeutic agents can provide better results when administered in combination with chemotherapy. There is an ongoing, phase II, single-arm trial assessing the efficacy of GEMCIS with pembrolizumab in patients with advanced biliary cancer (NCT03260712). Other studies have investigated the possible benefit of immune checkpoint inhibitors combined with locoregional therapeutic regimens (NCT02821754, NCT04299581).

Figure 4 presents a therapeutic algorithm that encompasses all the above described treatment modalities for iCCA.

## CONCLUSION

Increasing data during the last 5 years have strengthened the association between the infection with HBV and the development of iCCA. The epidemiological data unveiling this association are from both Eastern and Western countries and this linkage has been confirmed by multiple meta-analyses. In addition, the pathogenetic pathways through which HBV leads to the development of iCCA have been recently the targets of intense investigation. Furthermore, the diagnosis of iCCA in the setting of chronic liver

disease is frequently challenging and often requires histological examination. Nonetheless, certain aspects of this association still remain ill-defined.

In terms of management, the need for effective treatment modalities beyond SR is critical both in the first and the second line treatment. The evolution of personalized approaches through the recognition of specific therapeutic targets will improve the effectiveness of our treatment approaches. It is also likely that the results of ongoing studies in the field of immunotherapy will allow the use of this promising treatment in patients with iCCA, as well. Furthermore, it is currently unclear whether antiviral treatment for HBV can decrease the incidence of iCCA. Large, well-designed studies should address this important question. Focused research on these aspects of the management of HBV-associated iCCA in the future will enhance our ability to manage successfully this dreadful cancer.

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