Journal of Clinical and Translational Hepatology **2023** vol. 11(5) | 1106–1117
DOI: 10.14218/JCTH.2022.00141

Original Article

Intrahepatic Cholangiocarcinoma and Hepatocellular Carcinoma: Real-life Data on Liver Disease, Treatment and Prognosis

Xavier Adhoute[1*], Olivia Pietri[1], Guillaume Pénaranda[2], Thomas Wolf[1], Patrick Beaurain[3], Olivier Monnet[3], Arthur Laquière[1], Justine Bonomini[4], Frédéric Neumann[5], Olivier Levrel[5], Jean-Pascal Buono[5], Xavier Hanna[6], Paul Castellani[1], Hervé Perrier[1], Marc Bourliere[1] and Rodolphe Anty[7]

[1]Department of Gastroenterology and Hepatology, Hôpital Saint-Joseph, Marseille, France; [2]Department of Biostatistics, AlphaBio-Biogroup Laboratory, Marseille, France; [3]Department of Radiology, Hôpital Saint-Joseph, Marseille, France; [4]Department of Clinical Research, Hôpital Saint-Joseph, Marseille, France; [5]Medipath, Eguilles, France; [6]Department of Hepato-biliary Surgery, Hôpital Saint-Joseph, Marseille, France; [7]Department of Gastroenterology and Hepatology, Hôpital Universitaire de l'Archet, Nice, France

Received: 2 December 2022 | **Revised:** 16 March 2023 | **Accepted:** 23 March 2023 | **Published online:** 16 May 2023

Abstract

Background and Aims: Hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (iCCA) have common features and differences. This real-life study investigated their characteristics, treatment modalities, and prognoses. ***Methods:*** This retrospective comparative study was performed in 1,075 patients seen at one tertiary center between January 2008 and December 2020. Overall survival (OS) was estimated by the Kaplan-Meier method. Subclassification of iCCAs after histological and radiological review, and molecular profiling was performed. ***Results:*** HCCs patients were more likely to have early-stage disease than iCCA patients. iCCA patients were more likely to be female, especially those patients without cirrhosis (43% vs. 17%). Cirrhosis was prominent among HCC patients (89% vs. 34%), but no difference in underlying liver disease among cirrhotic patients was found. OS of HCC patients was 18.4 (95% CI: 6.4, 48.3) months, that of iCCA patients was 7.0 (95% CI: 3.4, 20.1) months. OS of Barcelona Clinic Liver Cancer C HCC patients was 7.8 (95% CI: 4.3, 14.2) months, that of advanced/metastatic iCCA patients was 8.5 (95% CI: 5.7, 12.3) months. In patients treated with sorafenib, OS was longer in HCC patients who received subsequent tyrosine kinase inhibitor therapies. No significant OS difference was found between iCCA patients with and without cirrhosis or according to histological subtype. A targetable molecular alteration was detected in 50% of the iCCA patients. ***Conclusions:*** In this French series, cirrhosis was common in iCCA, which showed etiological factors comparable to those of HCC, implying a distinct oncogenic pathway. Both entities had a dismal prognosis at advanced stages. However, systemic therapies sequencing in HCC and molecular profiling in iCCA offer new insights.

Citation of this article: Adhoute X, Pietri O, Pénaranda G, Wolf T, Beaurain P, Monnet O, *et al*. Intrahepatic Cholangiocarcinoma and Hepatocellular Carcinoma: Real-life Data on Liver Disease, Treatment and Prognosis. J Clin Transl Hepatol 2023;11(5):1106–1117. doi: 10.14218/JCTH.2022.00141.

Introduction

Intrahepatic cholangiocarcinoma (iCCA), or peripheral cholangiocarcinoma, is the second most common primary liver cancer after hepatocellular carcinoma (HCC).[1] Based on their geographical distribution, iCCAs can be rare or common malignancies related to specific risk factors.[2] The iCCA incidence has increased in recent years in Western countries, and the age-related death rate is higher in France than in other European countries.[3] iCCAs are tumors with a poor prognosis and are commonly diagnosed at an advanced stage.[4] Histological subclassification as well as molecular profiling of the tumors through genomic and transcriptomic analyses,[5] and the latest therapeutic advances will improve their management. Biliary tree cellular diversity as well as various hepatic and biliary risk factors leading to chronic inflammation and specific oncogenic dysregulation are probably responsible for the biliary tumor heterogeneity.[5] There are two major subtypes of iCCAs: those that arise from small ducts, which have nodular morphology and are associated with chronic liver disease, and those that arise from large ducts.[6] The latter iCCAs are morphologically different, mucinous, and resem-

Keywords: Intrahepatic cholangiocarcinoma; Hepatocellular carcinoma; Cirrhosis; NASH; Oncogenic alterations.

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; BRAF, v-raf murine sarcoma viral oncogene homolog B1; BRCA, Breast cancer gene; BTC, biliary tract cancer; CI, confidence interval; CisGem, cisplatin/gemcitabine; FOLFOX, 5-FU and LV plus Oxaliplatin; FGFR, fibroblast growth factor receptor; HER2, human epidermal growth factor receptor 2; HCC, Hepatocellular carcinoma; iCCA, Intrahepatic cholangiocarcinoma; IDH, isocitrate dehydrogenase; LD, Large-bile-duct; MET, mesenchymal epithelial transition factor receptor; MF, Mass forming; NAFLD, nonalcoholic fatty liver disease; OR, Odds ratio; OS, Overall survival; PDI, Periductal infiltrative; SD, Small-bile-duct; TACE, Transarterial chemoembolization; TKI, tyrosine kinase inhibitor.

[*]**Correspondence to:** Xavier Adhoute, Department of Gastroenterology and Hepatology, Hôpital Saint-Joseph, 26 Bd Louvain, Marseille 13008, France. ORCID: https://orcid.org/0000-0001-5977-800X. Tel: +33-491801220, Fax: +33-491255326, E-Mail: xvadhoute@gmail.com

ble juxta hilar CCAs histologically, and they are associated with cholangitis, flukes, and precursor lesions. Another major distinctive feature is that the two subtypes have unique oncogenic alterations.[5] The two most common primary liver cancers (HCC and iCCA) share common risk factors,[1] and may have similar radiological patterns.[7] Thus, we conducted a retrospective study to (1) investigate iCCA patient characteristics (especially underlying liver diseases) and those of HCC patients seen at the same center for more than a decade; (2) analyze treatment modalities and patient survival in these real-life cohorts; and (3) assess the impact of cirrhosis and histological subtype in the iCCA group as well as the presence of actionable oncogenic alterations.

Methods

Patients

This was a single-center retrospective study conducted from January 2008 to December 2020. The medical files of all consecutive patients enrolled in this period with a diagnosis of HCC or iCCA (recorded from 2010 onward) were considered for the study. Data were collected prospectively through an internal database and analyzed retrospectively. Our workup included systematic assessment to detect underlying liver disease for HCC or iCCA patients, supported by noninvasive measurement of liver stiffness by transient elastography and controlled attenuation parameters. The diagnosis of HCC was by radiology following international guidelines[8] or on histology in the absence of formal radiological criteria and in the absence of cirrhosis. HCC patients were classified according to the Barcelona Clinic Liver Cancer (BCLC) staging system. Those with a single nodule of >50 mm were designated as having BCLC stage AB disease. The treatment strategy was discussed during multidisciplinary concertation sessions, with recommendations based on the National Thesaurus of Digestive Cancerology (TNCD). Early tumors were treated with a curative approach or according to the stage migration concept.[8] Advanced HCCs with sectorial portal thrombosis were sometimes treated with an intra-arterial procedure such as transarterial chemoembolization (TACE) based on expert recommendations.[9] HCC patients who had transplantation as the first treatment were not included.

The diagnosis of iCCA was based on histology, and tumors were classified according to the eighth American Joint Committee on Cancer Staging System.[10] Patients with a diagnosis of combined hepatocellular-cholangiocarcinoma were excluded. The treatment options, especially iCCA resection, were discussed during multidisciplinary concertation sessions in accordance with the National Thesaurus of Digestive Cancerology recommendations at that time. Advanced iCCA was treated with systemic chemotherapy, a cisplatin/gemcitabine (CisGem) regimen,[11] or a combination of oxaliplatin, 5-FU and LV (FOLFOX) according to patient performance status (PS 0/1). If the PS was 2, the patient was treated with gemcitabine alone. Patients with unresectable iCCA without extrahepatic disease were sometimes treated with locoregional therapies [TACE or selective internal radiotherapy (SIRT)] in combination with systemic chemotherapy.

As part of this study, a histological review was performed to classify iCCA cases into the two main histopathological subtypes according to the size of the affected duct: small bile duct (SD), or large bile duct (mucinous) (LD). A radiological review was also performed on all iCCA cases, especially in histologically indeterminate iCCAs, to classify them according to gross appearance into the mass forming (MF) (mostly associated with SD iCCA) or periductal infiltrative (PDI) (+/− MF) subtype; the PDI subtype is exclusively seen with LD type iCCA. In addition to immunohistochemical study of tumor tissue to evaluate the protein expression of human epidermal growth factor receptor 2 (HER2) and to investigate the mismatch repair phenotype, we performed molecular profiling of iCCA patients to detect oncogenic molecular alterations targetable by therapies after gaining access to a molecular genetics platform in 2020. The platform employed tumor DNA and RNA targeted sequencing panels to detect activating mutations and chromosomal rearrangements, respectively. The Oncomine Focus Assay (Thermo Fisher Scientific, Waltham, MA, USA) was used to conduct concurrent DNA and RNA next-generation sequencing analysis from formalin-fixed paraffin-embedded samples, targeting 77 genes (mutations in 45 genes including BRAF, CDKN2A, EGFR, ERBB3, FGFR1, 2, 3, IDH1/2, KRAS, MET, NTRK1, 2, PIK3CA, PTEN, RAF-1, RET, TP53; fusions in 18 genes including EGFR, FGFR1, 2, 3, MET, NTRK1, 2, 3; copy number variations in 14 genes including EGFR, ERBB2 et 3, FGFR1, 2 et 3, KRAS, MET), and 15 genes that have various roles in the homologous DNA damage repair pathway (Oncomine BRCA Expanded panel). The current study was approved by the ethics committees of our institution. It followed the Good Clinical Practice guidelines and was conducted following the ethical principles of the Declaration of Helsinki.

Statistical analysis

Quantitative data were reported using the mean and standard deviation (SD); qualitative data were reported using the frequency and percentage. Quantitative data were compared between groups using Student's t test for normally distributed data or the nonparametric Wilcoxon test otherwise; the chi-squared test or Fisher's test was used for comparison of qualitative data. The Mantel-Haenszel chi-squared test was performed to compare ordinal scale data. Risk factors for HCC or iCCA were analyzed by univariate logistic regression analysis prior to multivariate logistic regression analysis. Items that were identified as significant in the univariate analysis were included in the multivariate model analysis. The multivariate results were reported using odds ratios (ORs) and 95% confidence intervals (CIs). Overall survival (OS) was defined as the time interval between the diagnosis of cancer and death or the time of last follow-up for patients who were still alive. Survival was compared between groups using the log-rank test. OS results were reported using median and interquartile range (q1, q3) and hazard ratios (HRs) and 95% CIs. All *p*-values were considered significant at α-level=0.05. All calculations were performed using SAS V9.4 statistical software (SAS Institute Inc., Cary, NC, USA).

Results

Characteristics of HCC and iCCA patients: descriptive study

Data from 1,075 patients were analyzed; 972 patients with HCC classified as BCLC stage A (45%, including 8% with a single nodule of >50 mm), B (18%), C (26%) or D (11%), and 103 patients with iCCA of the SD MF (62%) or LD PDI (38%) subtypes. HCCs (53%) and iCCAs (9%) were detected following systematic follow-up, based on symptoms (29% and 67% respectively), or incidentally (18% and 24% respectively). PS was better in the HCC group (Table 1). The two cohorts did not differ in mean age at diagnosis (67.7 years and 67.8 years, respectively) or mean body mass index (26.0 kg/m^2 and 26.3 kg/m^2, respectively), but there were more female iCCA (34%) than HCC (17%) patients,

Table 1. Baseline characteristics of patients with HCC or iCCA

Patient characteristics	HCC (*n*=972)	iCCA (*n*=103)
Age, years, mean (SD)	67.7 (11.0)	67.8 (11.1)
Sex, *n* (%)		
Male	805 (83)	68 (66)
Female	167 (17)	35 (34)
PS, *n* (%)		
0	543 (56)	29 (28)
1	188 (19)	49 (48)
>1	241 (25)	25 (24)
BMI, mean (SD)	26.0 (4.6)	26.3 (5.1)
Cirrhosis, *n* (%)		
Yes/No	868 (89)/104 (11)	35 (34)/68 (66)
Underlying liver diseases		
Etiology, *n* (%)		
Viral/Viral+Alcohol	358 (36.8)/56 (5.8)	14 (13.6)/2 (1.9)
Alcohol	301 (31)	20 (19.4)
NASH	178 (18.3)	29 (28.2)
Other	62 (6.4)	2 (1.9)
Healthy liver	17 (1.8)	36 (35)
Tumor histological confirmation, *n* (%)	361 (37)	103 (100)
Laboratory tests		
Albumin (g/L), mean (SD)	34.3 (7.1)	35.4 (7.2)
Bilirubin (μmol/L), mean (SD)	37.5 (147.8)	62.0 (116.7)
PT (%), mean (SD)	75.5 (17.0)	83.0 (17.5)
Platelets (10^9/L), mean (SD)	160 (92)	229 (92)
Alkaline phosphatase (U/L), mean (SD)	148.8 (129.2)	219.1 (218.1)
ASAT (U/L), mean (SD)	86.2 (110.0)	81.2 (96.2)
ALBI[‡] grade, *n* (%)		
1	209 (23.0)	28 (32.6)
2	531 (58.4)	41 (47.7)
3	170 (18.7)	17 (19.8)
AFP (ng/mL), median (q1, q3)	18 (5, 317)	3 (2, 14)
Tumor characteristics		
Largest tumor diameter mm, mean (SD)	52.4 (42.6)	73.9 (38.1)
Nodules[*], *n* (%)		
<3	635 (66.3)	52 (50)
≥3	323 (33.7)	51 (50)
Vascular invasion, *n* (%)		
No/Yes	717 (74)/255 (26)	59 (57)/44 (43)
Metastases, *n* (%)	36 (4)	43 (42)
Staging system for HCC: BCLC, *n* (%)	BCLC 0/A 359 (37); BCLC AB 75 (8); BCLC B 175 (18); BCLC C 254 (26); BCLC D 109 (11)	IA/B, *n*=27 (26); II, *n*=33 (32); IV, *n*=43 (42)
Staging system for iCCA: 8th AJCC, *n* (%)		
Treatment type, *n* (%)		
Curative treatment	308 (32)	20 (20)
Noncurative treatment	480 (49)	61 (59)
SC	184 (19)	22 (21)

The ALBI score was calculated as ($\log_{10}$ total bilirubin (mmol/L) × 0.66) + (albumin (g/L) × −0.085). ALBI grades were defined as 1 (score≤−2.60), 2 (score>−2.60 and ≤−1.39), and 3 (score>−1.39). [‡]ALBI grade data on 910 HCC patients and 86 iCCA patients. [*]Number of nodules (data on 958 HCC patients). AFP, alpha fetoprotein; AJCC, American Joint Committee on Cancer; ALBI, albumin-bilirubin; ASAT, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; BMI, body mass index; HCC, hepatocellular carcinoma; iCCA, intrahepatic cholangiocarcinoma; IU, international unit; NASH, nonalcoholic steatohepatitis; PS, performance status; PT, prothrombin time; SC, supportive care.

Table 2. iCCA: Characteristics of patients with or without liver cirrhosis

Patient characteristics	Cirrhotic patients (*n*=35)	Noncirrhotic patients (*n*=68)	*p*
Age, years, mean (SD)	67.4 (9.0)	67.7 (12.0)	0.6164
Sex, *n* (%)			0.0149
Male/Female	29 (83)/6 (17)	39 (57)/29 (43)	
PS 0/1/>1, *n* (%)	8 (23)/15 (43)/12 (34)	21 (31)/34 (50)/13 (19)	0.1231
BMI, mean (SD)	26.8 (5.3)	26.0 (5.0)	0.5435
Etiology, *n* (%)			<0.0001
Virus/Virus+Alcohol	9 (25.7)/2 (5.7)	5 (7.4)/0	
Alcohol	13 (37.1)	7 (10.2)	
NASH	9 (25.7)	20 (29.4)	
Other	2 (5.7)	14 (20.6)	
Healthy liver	0	22 (32.4)	
Laboratory tests			
Albumin (g/L), mean (SD)	35.7 (6.4)	35.2 (7.7)	0.7842
Bilirubin (µmol/L), mean (SD)	67.9 (118.4)	59.1 (116.7)	0.2421
PT (%), mean (SD)	79.1 (16.8)	84.9 (17.7)	0.0825
Platelets (10^9/L), mean (SD)	192 (101)	246 (83)	0.0054
Alkaline phosphatase (U/L), mean (SD)	183 (123)	234 (247)	0.5021
ASAT (U/L), mean (SD)	104.8 (133.6)	71.6 (75.1)	0.2232
ALBI[‡] grade, *n* (%)			0.3339
1	7 (24)	21 (37)	
2	17 (59)	24 (42)	
3	5 (17)	12 (21)	
CA19.9 (U/mL), mean (SD)	4,566 (11,015)	2,551 (6,491)	0.7229
Tumor characteristics			
Largest tumor diameter mm, mean (SD)	75.0 (42.6)	73.4 (36.0)	0.8175
Nodules, *n* (%)			0.0929
<3	14 (38%)	38 (56%)	
≥3	21 (62%)	30 (44%)	
Vascular invasion, *n* (%)			0.0007
No/Yes	12 (34)/23 (66)	47 (69)/21 (31)	
Metastases, *n* (%)	14 (40)	29 (43)	0.7964
Treatment type, *n* (%)			0.1166
Curative treatment	4 (11)	16 (24)	
Noncurative treatment	20 (57)	41 (60)	
Supportive care	11 (31)	11 (16)	

[‡]ALBI grade (data on 29 cirrhotic patients; data on 57 noncirrhotic patients). ALBI, albumin-bilirubin; ASAT, aspartate aminotransferase; BMI, body mass index; IU, international unit; NASH, nonalcoholic steatohepatitis; PS, performance status; PT, prothrombin time; SC, supportive care.

especially in those without cirrhosis (43% vs. 17% among iCCA patients with cirrhosis; Tables 1 and 2). Cirrhosis was more common in the HCC group (89% compared with 34%), but there was no difference in liver disease etiology among cirrhotic patients between the two groups (HCC: viral 38.8%, alcohol 33.1%, nonalcoholic steatohepatitis 16.4% vs. iCCA: 25.7%, 37.1%, 25.7%, respectively; p=0.4763; Table 3). Most patients with cirrhosis had preserved liver function assessed by Child-Pugh score and ALBI grade in each cohort. Esophageal varices were described in 49.6% of patients in the HCC group vs. 20% of iCCA patients with cirrhosis. Regarding tumor characteristics, the iCCA group had larger tumor diameters at diagnosis, more multinodular tumors, greater vascular invasion and more patients with metastases.

Characteristics of iCCA patients with and without cirrhosis: comparative study

Apart from male sex and underlying viral or alcohol-related

Table 3. Baseline characteristics of cirrhotic patients with HCC or iCCA

Characteristics	HCC (*n*=868)	iCCA (*n*=35)
Age, years, mean (SD)	67.3 (10.7)	67.4 (9.0)
Sex, *n* (%)		
Male	724 (83)	29 (83)
Female	144 (17)	6 (17)
PS, *n* (%)		
0	473 (54)	8 (23)
1	164 (19)	15 (43)
>1	231 (27)	12 (34)
BMI, mean (SD)	26.0 (4.6)	26.8 (5.3)
Cirrhosis etiology, *n* (%)		
Viral/Virus+Alcohol	337 (38.8)/55 (6.3)	9 (25.7)/2 (5.7)
Alcohol	287 (33.1)	13 (37.1)
NASH	142 (16.4)	9 (25.7)
Other	47 (5.4)	2 (5.7)
EV[¥], *n* (%)		
No EV	341 (50.4)	28 (80)
Grade 1	124 (18.3)	2 (6)
Grade 2/3	212 (31.3)	5 (14)
[#]Child-Pugh score, *n* (%)		
A	536 (65)	20 (69)
B	274 (34)	8 (27.5)
C	10 (1)	1 (3.5)
Laboratory tests		
Albumin (g/L), mean (SD)	34.0 (7.0)	35.7 (6.4)
Bilirubin (µmol/L), mean (SD)	40.2 (156.2)	67.9 (118.4)
PT (%), mean (SD)	73.9% (16.8)	79.1 (16.8)
Platelets (10^9/L), mean (SD)	150.1 (88.0)	192.0 (101.3)
AP (U/L), mean (SD)	151.1 (130.7)	183.1 (123.3)
ASAT (U/L), mean (SD)	88.1 (112.3)	104.8 (133.6)
ALBI[‡] grade, *n* (%)		
1	167 (20)	7 (24)
2	489 (60)	17 (59)
3	164 (20)	5 (17)
AFP (ng/mL), mean (SD)	5,560 (39,811)	3,581 (19,547)
Tumor characteristics		
Largest tumor diameter mm, mean (SD)	49.4 (40.9)	75.0 (42.6)
Nodules[*], *n* (%)		
<3	548 (64)	13 (38)
≥3	308 (36)	21 (62)
Vascular invasion, *n* (%)		
No	627 (72)	12 (34%
Yes	241 (28)	23 (66)
Metastases, *n* (%)	33 (4)	14 (40)
Treatment type, *n* (%)		
Curative treatment	236 (27)	4 (11)
Noncurative treatment	458 (53)	20 (57)
SC	174 (20)	11 (31)

The ALBI score was calculated as ($\log_{10}$ total bilirubin (mmol/L) × 0.66) + (albumin (g/L) × −0.085). ALBI grades were defined as 1 (score≤−2.60), 2 (score>−2.60 and ≤−1.39), and 3 (score>−1.39). [¥]Esophageal varices (data on 677 HCC patients). [#]Child-Pugh score (data on 820 HCC patients; data on 29 iCCA patients). [‡]ALBI grade (data on 820 HCC patients; data on 29 iCCA patients). Nodules[*] (data on 856 HCC patients; data on 34 iCCA patients). AFP, alpha fetoprotein; ALBI, albumin-bilirubin; ASAT, aspartate aminotransferase; BMI, body mass index; EV, esophageal varices; HCC, hepatocellular carcinoma; iCCA, intrahepatic cholangiocarcinoma; IU, international unit; NASH, nonalcoholic steatohepatitis; PS, performance status; PT, prothrombin time; SC, supportive care.

liver disease being overrepresented in the cirrhosis group, there was no significant difference in age at diagnosis, tumor diameter, multinodularity, CA19-9 serum level, or liver function between the groups (Table 2). There was more vascular invasion in the cirrhosis group.

Characteristics of iCCA patients with the SD MF or LD PDI subtype: comparative study

The comparative study of SD MF iCCAs and LD PDI iCCAs showed that the SD group had more women, but the LD group had higher rates of cholestasis and aspartate aminotransferase serum levels as well as lower serum albumin and more frequent vascular invasion (Table 4).

Treatment modalities and survival of HCC and iCCA patients

HCC patients: The first-line treatment modalities used are shown in Figure 1. Most patients with early HCC (60% (BCLC stage 0/A+AB), *n*=260) received curative treatment. TACE was the primary treatment modality for BCLC stage B HCC (64%, *n*=112). Patients with advanced HCC were primarily treated with sorafenib (44%, *n*=113) or with intra-arterial procedures, most commonly TACE (30%, *n*=77). Treatment allocation was driven by baseline liver function.[12] Most HCC patients with Child-Pugh B liver function were only suitable for noncurative or supportive care (Supplementary Table 1). The mean follow-up of HCC patients was 27.2±30.1 months. The OS of BCLC stage A patients (47 months) was significantly better than that of BCLC stage B, C and D patients ($p<0.0001$; Fig. 2). The OS of HCC patients treated with surgical resection was significantly better than that of HCC patients treated with other modalities for early (including single tumors >50 mm) or intermediate-stage disease, especially compared with that of HCC patients treated with TACE (Table 5). Regarding advanced HCC, there was no significant difference in OS between patients treated with intra-arterial procedures and those treated with sorafenib as the primary treatment modality (Table 5). However, the analysis of a larger cohort of patients treated with sorafenib, including those who received subsequent tyrosine kinase inhibitor (TKI) therapies (regorafenib or cabozantinib, *n*=253; Supplementary Fig. 1), had a significantly better OS, sorafenib 6.7 (95% CI: 3.9, 11.9) months vs. TKIs 15.2 (95% CI: 6.2, 32.8) months, $p=0.0009$.

iCCA patients: Regarding the iCCA group, less than a quarter of patients underwent curative surgical resection (Fig. 1). Nearly half of the patients received systemic chemotherapy (46%, *n*=47), mostly the CisGem regimen (*n*=31), the FOLFOX regimen (*n*=8), or gemcitabine alone (*n*=8). Ten percent of patients were treated with a locoregional intra-arterial procedure. There was no significant difference in the therapeutic strategy for iCCA patients with and without cirrhosis (Table 2). More than one-third of the patients with LD PDI iCCA were ineligible for specific treatment (Table 4).

The mean follow-up of iCCA patients was 12.1±12.7 months. The OS of iCCA patients who underwent surgical procedures (*n*=20) was 21.8 (±12.4, 34.2) months, while that of iCCA patients who were treated with noncurative procedures (*n*=61) was 8.5 (5.7, 12.3) months ($p=0.0270$). The OS of iCCA patients treated with systemic chemotherapy was 7.8 (95% CI: 5.9, 12.0) months. The OS of iCCA patients with or without cirrhosis across all treatments was not significantly different: 9.0 (95% CI: 5.0, 12.3) vs. 11.0 (95% CI: 5.9, 25.0) months, $p=0.1633$. The OS of iCCA patients with SD MF vs. LD PDI iCCA across all treatments was not significantly different: 10.1 (95% CI: 5.8, 21.0) months vs. 9.0 (95% CI: 5.6, 32.4) months, $p=0.7570$.

HCC and iCCA patients - survival analysis: The OS of HCC patients (*n*=972) was 18.4 (95% CI: 6.4, 48.3) months and that of iCCA patients (*n*=103) was 7.0 (95% CI: 3.4, 20.1) months. The OS of BCLC stage C HCC patients (*n*=208) was 7.8 (95% CI: 4.3, 14.2) months and that of locally advanced/metastatic iCCA patients (*n*=61) was 8.5 (95% CI: 5.7, 12.3) months. Both groups had a similar proportion of patients who were exclusively eligible for supportive care (HCC 19% vs. iCCA 21%; Fig. 1).

iCCA patient genomic profile: Molecular cholangiocarcinoma profiling could be performed in 18 patients: patients experiencing recurrence after surgery (*n*=7) and patients with unresectable iCCA treated by first-line locoregional (2) or systemic (*n*=9) therapies. Large-scale genomic and transcriptomic analysis found an actionable molecular alteration targetable by therapy in 50% of 18 iCCA patients (Table 6). iCCA patients harbored alterations in the isocitrate dehydrogenase 1 (IDH1) and fibroblast growth factor receptor 3 (FGFR3) genes, genes in the Ras/phosphatidylinositol 3-kinase (PI3-kinase) pathway (v-raf murine sarcoma viral oncogene homolog B1 (BRAF), mesenchymal epithelial transition factor receptor (MET), and HER2), chromatin regulator genes [BReast CAncer gene 1 (BRCA1)], and genes involved in the DNA mismatch repair system. Other oncogenic alterations in cell cycle genes and DNA repair or chromatin regulators without targeted treatment options were also identified.

Discussion

In this retrospective study from a liver unit, a comparative analysis found differences and similarities among HCC and iCCA patients. We found a higher proportion of HCC patients in this French cohort of patients with primary hepatobiliary tumors. Most patients with HCC were detected as opposed to iCCA patients. However, this trend may change over time, as the main risk factor for iCCA in this series was chronic liver disease with cirrhosis, which was found in more than one-third of the study participants.

iCCAs represent approximately 15% of primary liver cancers.[1] The results of this study were in line with that finding, and other features associated with iCCA, such as female sex, multinodularity, and the presence of metastases, were identified, as in other series.[4,13] The overrepresentation of women in the iCCA group compared to the HCC group in our series was found in iCCA patients without cirrhosis. Female sex was independently associated with iCCA diagnosis in a study by Lee *et al*.[4] We also found an overrepresentation of females in iCCA in phase 2 and 3 trials evaluating targeted therapies for iCCA patients with specific genomic alterations (ClarIDHy[14] (ivosidenib): 65%, FIGHT-202[15] (pemigatinib): 58%, NCT02150967[16] (infigratinib): 57%) and in the phase 3 TOPAZ-1 study[17] (50%), in which 55% of the patients had iCCA. However, we found a similar sex distribution among cirrhotic patients in the HCC and iCCA groups, and there was a male predominance. The result is not surprising, as the risk factors associated with cirrhosis (notably alcohol) affect more men. Multinodularity and extrahepatic spread are classically associated with iCCA.[4] Indeed, iCCA is characterized by lack of a capsule and a significant fibrous stroma,[18] with effector cells such as tumor-associated macrophages,[19] and activated myofibroblasts[20] that are driven by cytokines and growth factors such as transforming growth factor-beta (TGF-β) secreted by tumor cells.

In our European series, we found that a large majority of HCC patients had cirrhosis. More than 30% of patients in the iCCA group had cirrhosis, which is a well-documented risk factor in that pathology.[1,2] The finding is consistent

Table 4. Characteristics of patients with SD vs. LD iCCA

iCCA patient characteristics	SD MF (*n*=64)	LD PDI (*n*=39)	*p*
Age, years, mean (SD)	67.5 (11.2)	67.6 (10.9)	0.9149
Sex, *n* (%)			0.0319
Male/Female	37 (58)/27 (42)	31 (79)/8 (21)	
PS 0/1/>1, *n* (%)	19 (30)/33 (51)/12 (19)	10 (26)/16 (41)/13 (33)	0.2047
BMI, mean (SD)	26.2 (5.2)	26.5 (4.9)	0.7705
Etiology, *n* (%)			0.2169
Virus/Virus+Alcohol	11 (17.2)/1 (1.6)	3 (7.7)/1 (2.6)	
Alcohol	8 (12.5)	12 (30.8)	
NASH	18 (28.1)	11 (28.2)	
Other	10 (15.6)	5 (15.4)	
Healthy liver	16 (25.0)	6 (15.4)	
Cirrhosis, *n* (%)			0.2386
No/Yes	45 (70)/19 (30)	23 (59)/16 (41)	
OV, *n* (%)			0.4081
No/Yes	19 (86)/3 (14)	11 (73)/4 (27)	
Laboratory tests			
Albumin (g/L), mean (SD)	37.1 (7.4)	32.9 (6.4)	0.0077
Bilirubin (μmol/L), mean (SD)	16.3 (12.9)	132.5 (162.9)	<0.0001
PT (%), mean (SD)	84.9 (15.0)	80.0 (20.8)	0.6162
Platelets (10^9/L), mean (SD)	237 (81)	216 (108)	0.3417
Alkaline phosphatase (U/L), mean (SD)	164.1 (91.5)	307.7 (315.8)	0.0140
ASAT (U/L), mean (SD)	63.2 (86.8)	110.2 (104.5)	0.0094
ALBI‡ grade, *n* (%)			0.0004
1	23 (45.1)	5 (14.3)	
2	23 (45.1)	18 (51.4)	
3	5 (9.81)	12 (34.3)	
CA19.9 (U/mL), mean (SD)	1,858 (6,475)	5,899 (10,646)	0.1984
Tumor characteristics			
Largest tumor diameter mm, mean (SD)	79.0 (39.4)	65.5 (34.6)	0.0926
Nodules, *n* (%)			0.2192
<3	29 (45.3)	22 (56.5)	
≥3	35 (54.7)	17 (43.5)	
Vascular invasion, *n* (%)			0.0283
No/Yes	42 (66)/22 (34)	17 (44)/22 (56)	
Metastases	27 (42)	16 (39)	0.9077
Treatment type, *n* (%)			0.0120
Curative treatment	12 (19)	8 (21)	
Noncurative treatment	44 (69)	17 (44)	
Supportive care	8 (12)	14 (36)	

‡ALBI grade (data on 51 SD MF iCCA patients; data on 35 LD PDI iCCA patients). ALBI, albumin-bilirubin; ASAT, aspartate aminotransferase; BMI, body mass index; IU, international unit; LD, large duct; MF, mass forming; NASH, nonalcoholic steatohepatitis; PDI, periductal infiltrative; PS, performance status; PT, prothrombin time; SD, small duct; SC, supportive care.

with other studies.[4,21] In an Italian multicenter series from expert centers, nearly half of the patients with iCCA (46%) had cirrhosis, and most of them were detected.[22] Thus, there may have been an underestimation.[21] Conversely, in phase 2/3 trials evaluating targeted therapies or the combination of chemotherapy plus immunotherapy as treatment for advanced iCCA, there have been few[14] or no cirrhotic patients, or data on cirrhosis have not been available.[15-17] The associ-

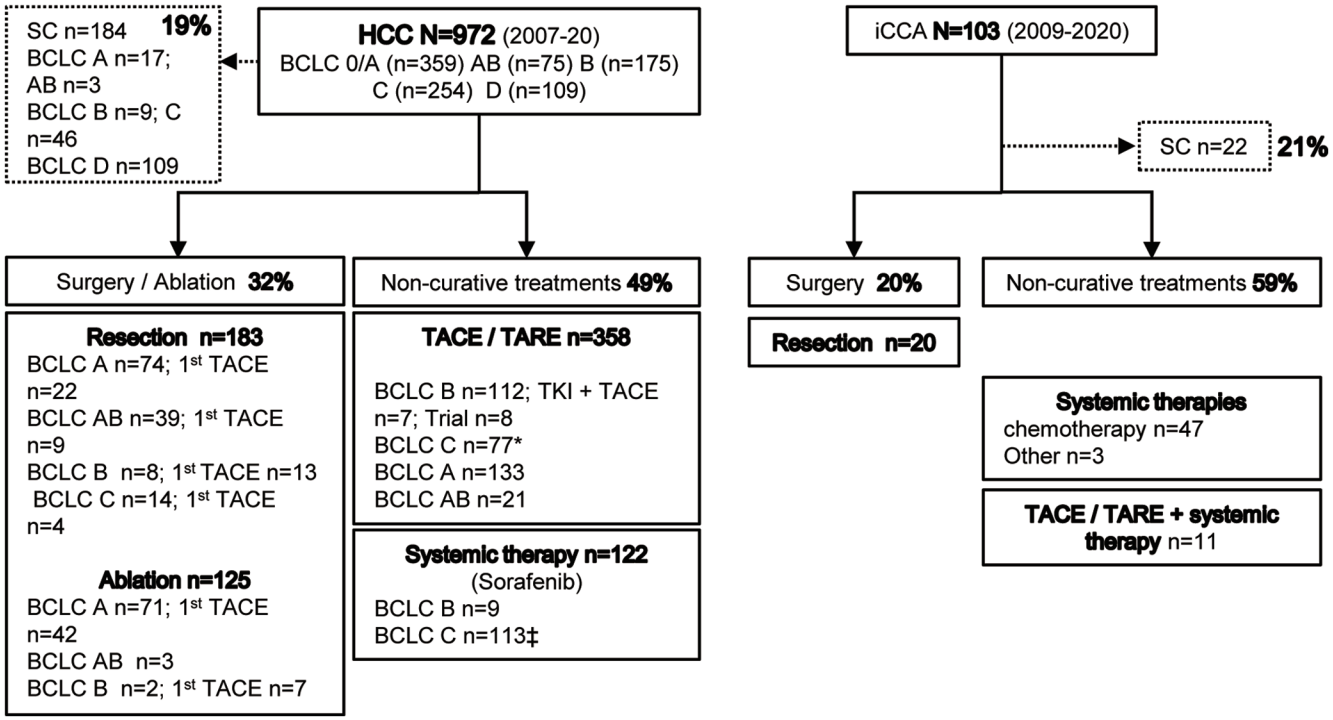

Fig. 1. First-line treatment modalities in patients with HCC or iCCA. *Including seven treated by TARE. ‡Plus radiation therapy *n*=2. HCC with noncirrhotic liver includes 17 patients with healthy liver and 87 patients with underlying liver fibrosis. HCC, hepatocellular carcinoma; iCCA, intrahepatic cholangiocarcinoma; BCLC, Barcelona Clinic Liver Cancer; SC, supportive care; TACE, transarterial chemoembolization; TKI, tyrosine kinase inhibitor; TARE, transarterial radioembolization.

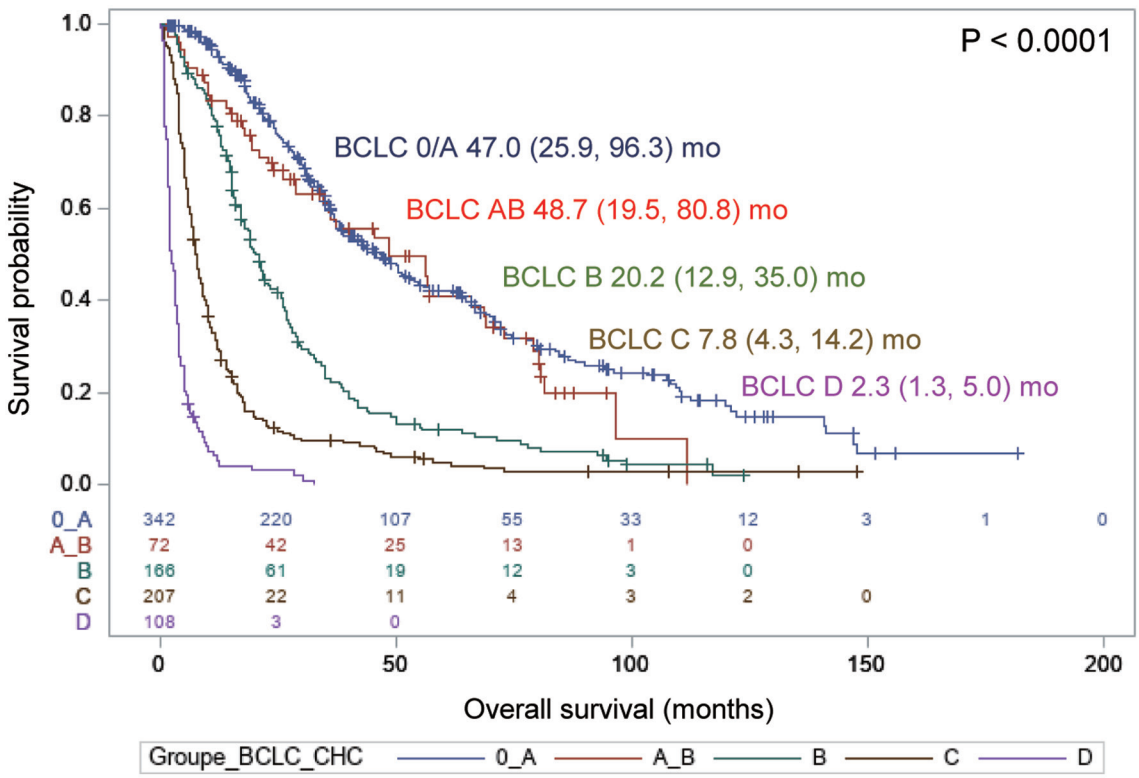

Fig. 2. Kaplan-Meier survival curves of patients with HCC classified according to the BCLC staging system. BCLC, Barcelona Clinic Liver Cancer; Mo, months. Data on 895 HCC. The survival time could not be calculated for 77 patients because of missing date of last follow-up.

Table 5. Survival of HCC patients according to BCLC stage and treatment modality

BCLC stage	OS (95% CI) - months	*p*-value (log-rank)	HR (95% CI)	*p*-value
BCLC 0/A		<0.0001		
TACE (*n*=133)	33.9 (19.2, 52.4)		Ref	
Resection (*n*=74)	109.3 (47.9, n.e.)		0.27 (0.17, 0.42)	<0.0001
Ablation+TACE (*n*=63)	74.6 (32.4, 147.0)		0.36 (0.24, 0.53)	<0.0001
Ablation (*n*=71)	47.0 (26.6, 83.7)		0.62 (0.43, 0.90)	0.0104
BCLC A/B		0.0001		
TACE (*n*=21)	26.0 (17.3, 37.3)		Ref	
Resection (*n*=39)	72.9 (48.6, 96.6)		0.33 (0.17, 0.64)	0.0010
Resection+1st TACE (*n*=9)	56.4 (28.9, n.e.)		0.45 (0.18, 1.14)	0.0918
BCLC B		0.0109		
TACE (*n*=112)	18.0 (11.2, 31.9)		Ref	
Resection±1st TACE (*n*=21)	26.9 (17.8, 55.6)		0.54 (0.36, 0.82)	0.0037
BCLC C		0.1111		
TACE (*n*=77)	8.1 (5.0, 15.0)		Ref	
Sorafenib (*n*=113)	6.7 (3.9, 11.9)		1.35 (1.01, 1.82)	0.0465

BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; n.e., not estimable; OS, overall survival; Ref, reference; TACE, transarterial chemoembolization.

ation of iCCA with cirrhosis raises several questions. Cirrhotic patients can develop either cancer, which highlights the absolute necessity of histological assessment if the radiological criteria for HCC are not fulfilled.[23] Histological confirmation is even more important given the potential identification of therapeutic targets in cholangiocarcinoma (Table 6). Cirrhosis was the main risk factor for iCCA in our series, and as previously reported,[24] cirrhosis, chronic hepatitis, alcohol use, and NASH were not associated with the iCCA subtype. The association of iCCA development with cirrhosis may allow earlier detection of this poor prognosis cancer[13] and identification of a target population that can benefit from curative

Table 6. Results of large-scale genomic and transcriptomic analysis of 18 patients with iCCA

Potentially actionable oncogenic alterations	ESCAT score	Patients eligible for potential targeted therapy	Matched targeted treatment administered
IDH1 mutations	IA	Pt n°1; Pt n°2	None
MSI	IC	Pt n°3	None
BRAF mutations	IIB	Pt n°4*	None
ERBB2 (*HER2*) amplifications, mutations	IIIIA	Pt n°5*, Pt n°6*	None
PIK3CA mutations	IIIA	Pt n°7	None
BRCA 1 mutations	IIIA	Pt n°8	None
MET mutations	IIIA	Pt n°5	None
FGFR3 mutations	IIIA	Pt n°9	None
Other oncogenic alterations			
CDKN2A/B loss		Pt n°3; Pt n° 4*	
TP53 mutations		Pt n°9; Pt n°3; Pt n°10	
NF1 mutations		Pt n° 4*	
ARID1A mutations		Pt n° 4*; Pt n° 7	
KRAS G12D mutation		Pt n° 11	
No oncogenic alterations		Pt n°12*; Pt n°13*; Pt n°14; Pt n° 15; Pt n°16; Pt n°17*; Pt n°18*	

*Cirrhotic patients. ARID1A, AT-rich interaction domain 1A; BRAF, v-raf murine sarcoma viral oncogene homolog B1; BRCA, BReast CAncer gene; CDKN2A/B, cyclin-dependent kinase inhibitor 2A/B; ESMO, European Society for Medical Oncology; ERBB2, erb-b2 receptor tyrosine kinase 2; ESCAT, Scale for Clinical Actionability of Molecular Targets; FGFR2, fibroblast growth factor receptor 2; HER2, human epidermal growth factor receptor 2; IDH, isocitrate dehydrogenase; KRAS, Kirsten rat sarcoma virus; MET, mesenchymal epithelial transition factor receptor; MSI, microsatellite instability; NF1, neurofibromin 1; PIK3CA, phosphatidylinositol 3-kinase catalytic subunit alpha; Pt, patient; TP53, tumor protein 53.

therapeutic options.[25] Moreover, in previous studies, cirrhosis did not affect the prognosis of patients with iCCA.[21,22] These results are not surprising, as liver function and tumor features (tumor size and metastatic spread) were comparable between our two iCCA subgroups with or without cirrhosis. Of course, these results should be interpreted with caution given the small sample size.

Our comparative analysis of HCC and iCCA found similar underlying liver diseases among cirrhotic patients. While cirrhotic patients are at risk of developing these two cancers, this result highlights the close link between these two entities and the importance of chronic inflammation related to hepatitis.[1] Common nucleotide substitutions in HCC and iCCA related to chronic hepatitis have been described.[26] The same study showed a similar gene expression profile (RNA-seq analysis) of biliary cancers and poorly differentiated HCC. The result suggests that the diseases involve activation of different oncogenic pathways but may have common cells of origin, although the last point remains controversial.[5] Indeed, biliary tree cells harbor different cell types, including hepatocytes, liver progenitor cells (which have a biphenotypic orientation), and biliary epithelial cells (mature nonmucin-producing interlobular cholangiocytes, and cylindrical mucin-producing cholangiocytes located in LDs). In addition to this cellular diversity, mature hepatocytes maintain phenotypic plasticity and thus an ability to differentiate into cholangiocytes. Activation of the Notch pathway or Ras/MAPK cascade and Tp53 mutations has been implicated in the conversion of normal hepatocytes into malignant cholangiocytes.[27,28] Thus, the similarities and heterogeneity of hepatobiliary tumors are substantial challenges that need to be considered.[5] In addition to iCCA and HCC, there are other rare liver cancers with biliary phenotypes.[29]

Nearly 20% of the HCC patients in our series had nonalcoholic fatty liver disease (NAFLD), and nearly one-third in the iCCA group had NAFLD. The results are not unexpected since these diseases have been recognized as major causes of chronic liver disease, the incidence of which is increasing.[30] Steatosis may be complicated by necrotic-inflammatory processes, which characterizes patients with NASH. Previous studies have shown a change in HCC tumor phenotype after TACE with the development of hepatobiliary cancers, suggesting the importance of necrosis in this process.[31] Necroptosis, which is programmed cell necrosis resulting in plasma membrane disruption following osmotic shock, appears to be particularly important in NAFLD and NASH.[32] Cells undergoing necroptosis release damage-associated molecular patterns that may shape the microenvironment through specific cytokine delivery by immune cells. A recent study underlines the influence of the microenvironment and necroptosis in biliary or hepatic cancers related to singular epigenetic regulators.[33] Thus, specific oncogenes and the tumor microenvironment drive the liver cancer phenotype.

In line with other studies,[4] our study found that therapeutic strategies differ between iCCA and HCC. A curative approach is more frequently used for HCC patients because one majority is detected. Some experts consider surgery the most effective treatment modality to achieve the best survival rate in HCC cases up to intermediate stage.[34] Moreover, the latest version of the BCLC staging system no longer recommends TACE as the main modality for intermediate-stage disease treatment.[35] In our series, stratification according to the BCLC system found tumors with different prognoses. However, BCLC stage AB HCC had a comparable prognosis with BCLC stage 0/A HCC, in contrast with the findings of other studies,[36] probably owing to the different treatment modalities within each group. The poor OS seen with sorafenib treatment is comparable to that seen in other real-life cohorts,[37] as the populations of patients have differed in trials.[38] Moreover, there was no survival benefit following the use of any endovascular procedure, mainly TACE, as an alternative therapeutic option for advanced HCC. These results should be interpreted with caution in the absence of comparison using propensity score matching. Conversely, survival was longer in the sorafenib group treated with second-line TKI therapy, and survival with sorafenib would likely be better over time.[38] Once again, the results should be interpreted with caution in the absence of comparison using propensity score matching; however, sequencing of systemic therapies can provide a survival benefit for HCC patients,[39] although this strategy can be used in relatively few patients in the TKI era.[40]

Regarding the iCCA population, our series did not find a significant difference in prognosis between patients with SD iCCA and those with LD iCCA across all treatments despite there being more impaired liver function in the LD group. However, more than one-third of patients with LD iCCA were ineligible for specific treatment. Studies have shown that these two entities differ radiologically and histologically[6] and regarding molecular alterations[5] and treatment response.[41] The LD iCCA subtype is characterized by higher rates of desmoplastic stroma and higher frequencies of TGF-β1 pathway gene alterations and Tp53 and KRAS mutations.[41] LD iCCAs appear to have lower sensitivity to chemotherapy than SD iCCAs and they also reportedly show resistance to anti-PD1/PD-L1 immunotherapy[41] related to the suppressive immune microenvironment in KRAS-altered tumors. Given the results of the TOPAZ-1 trial,[17] which supports the combination of chemotherapy (CisGem regimen) plus anti-programmed death ligand 1 (PDL1) therapy (durvalumab), the management strategy for advanced iCCAs is about to change. This new combination may overcome such resistance. Furthermore, classification according to iCCA subtype is necessary to improve outcomes.

The difference in survival between HCC and iCCA patients is not unexpected and probably reflects the absence of screening in the iCCA group, which had a higher tumor burden than the HCC group (as has been previously reported), along with the difference in follow-up time. The difference was also likely related to the difference in curative approach rate in our series, as more patients in the HCC group were treated with curative strategies (32% vs. 20%). Moreover, the overall prognosis of advanced stage iCCA and HCC remains poor, together with comparable proportions of patients eligible for only palliative care. The situation is even more serious, as pointed out in a recent study conducted in all French hospitals, since most iCCA patients diagnosed during the period 2014–2015 only received supportive care.[13]

Chemotherapy with the CisGem regimen has been the only therapeutic approach for advanced biliary tract cancer (BTC) for many years and has produced modest results,[11] as reflected by our series. Intensification of chemotherapy has not shown any benefit,[42] and the use of new cytotoxics is under investigation. There is significant improvement with the combination of chemotherapy and immunotherapy.[17] Moreover, the prognosis of BTC, especially iCCA, is likely to change thanks to personalized therapeutic approaches. In our study, 50% of the patients in whom genomic and transcriptomic studies were performed had a targetable molecular alteration (Table 6). Large-scale sequencing technologies have highlighted BTC heterogeneity along with various oncogenic alterations that may be targeted by therapies. These molecular alterations (mutations, rearrangements, and amplifications) are diverse and affect many cellular processes.[5] The most commonly affected genes are those encoding the isocitrate

dehydrogenase 1 (IDH1) and IDH2 enzymes (the mutations of which are mutually exclusive) involved in DNA repair mechanisms and epigenetic regulation and those encoding fibroblast growth factors, which are associated with the SD iCCA subtype (mutations seen in approximately <5–20% of patients). These aberrations also less commonly affect pathway kinase genes (BRAF, MET, and ERBB2), chromatin remodeling genes (ARID1A) and mismatch repair genes (MLH1 and MSH2, or the germline mutations of BRCA1 and BRCA2 that we identified in our patients). Several targeted therapies are now approved by the Food and Drug Administration and European Medicines Agency for patients with cholangiocarcinoma who harbor specific genomic alterations. The prescription of these agents is now facilitated and prioritized by the European Medical Oncology Society (ESMO) Scale for Clinical Actionability of Molecular Targets (ESCAT) system.[43] Thus, tumor genetic testing should be performed as soon as the first systemic treatment is given and in the case of failure or progression.

This study suffers from limitations related to several factors: (1) It was a retrospective study, and we tried to reduce the relevant limitations by prospectively accessing data from our regular multidisciplinary collegial sessions. (2) We used histological review to classify the iCCA subtypes, as most of the biopsies were tumor biopsies and not surgical specimens. (3) There was a lack of data regarding the combination of anti-PD-L1 therapy (atezolizumab) plus anti-VEGF therapy (bevacizumab), which is the new standard of care for advanced HCC.[44] The combination of atezolizumab and bevacizumab was not available in France until 2020. 4) Finally, there was a lack of propensity score matching for some comparisons among HCC patients.

Conclusions

In this French series, cirrhosis was prominent in HCC and was also common in iCCA. The two diseases had similar etiological factors, suggesting a close relationship between the two entities. Thus, iCCA detection should be performed in patients with hepatobiliary tumors and cirrhosis through diagnostic biopsy. Cirrhosis did not affect iCCA prognosis in our series. Histological subclassification of iCCA resulted in distinct patient profiles and should be applied in daily practice. Both primary liver cancers had a comparable prognosis at an advanced stage. However, systemic therapies sequencing in HCC and molecular profiling of iCCAs with its potential therapeutic targets may reveal new therapeutic strategies.

Funding

None to decalre.

Conflict of interest

XA: Board member, Consultancy (Bayer, Ipsen, Eisai, Servier); PC: Consultancy (Gilead, Abbvie); MB: Board member, Consultancy (Merck-Schering Plow, Gilead, Janssen, Vertex, Boehringer-Ingelheim, BMS, Roche, Abbvie, GSK); HP: Consultancy (Sanofi); RA: Board member, Consultancy (Gilead, Bayer, Eisai, Intercept, Abbvie, MSD, Ipsen); OP: Abbvie, Gilead; AL: Boston Scientific. GP, JB, TW, PB, OM, FN, OL, JPB and XH have no conflict of interests related to this publication.

Author contributions

Study concept and design (XA, OP, RA, GP), investigation (XA, PO, TW, AL, PC, HP, XH, MB, OM, PB, FN, OL, JPB), acquisition of data (XA, OP, TW), analysis and interpretation of data (GP), drafting of the manuscript (XA, JB, RA), critical revision of the manuscript for important intellectual content (XA, JB, RA), and study supervision (XA). All authors have made a significant contribution to this study and have approved the final manuscript.

Ethical statement

This study did not involve humans, and only analyzed already recorded data. This study falls within the scope of the French Reference Methodology MR-004 (according to the 2016-41 law dated 26 January 2016 on the modernization of the French health system). As requested by the French regulations for such noninterventional studies, all patients were informed about the use of their data for research studies. The study was conducted in accordance with the ethical guidelines of the 1975 Declaration of Helsinki. In addition, the study was approved by the internal ethical review boards of the Saint Joseph Hospital of Marseille on March 7, 2022.

Data sharing statement

No additional data are available.

References

[1] Massarweh NN, El-Serag HB. Epidemiology of Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma. Cancer Control 2017;24(3):1073274817729245. doi:10.1177/1073274817729245, PMID:28975830.
[2] Palmer WC, Patel T. Are common factors involved in the pathogenesis of primary liver cancers? A meta-analysis of risk factors for intrahepatic cholangiocarcinoma. J Hepatol 2012;57(1):69–76. doi:10.1016/j.jhep.2012.02.022, PMID:22420979.
[3] Bertuccio P, Malvezzi M, Carioli G, Hashim D, Boffetta P, El-Serag HB, *et al*. Global trends in mortality from intrahepatic and extrahepatic cholangiocarcinoma. J Hepatol 2019;71(1):104–114. doi:10.1016/j.jhep.2019.03.013, PMID:30910538.
[4] Lee YT, Wang JJ, Luu M, Noureddin M, Nissen NN, Patel TC, *et al*. Comparison of Clinical Features and Outcomes Between Intrahepatic Cholangiocarcinoma and Hepatocellular Carcinoma in the United States. Hepatology 2021;74(5):2622–2632. doi:10.1002/hep.32007, PMID:34114675.
[5] Bragazzi MC, Ridola L, Safarikia S, Matteo SD, Costantini D, Nevi L, *et al*. New insights into cholangiocarcinoma: multiple stems and related cell lineages of origin. Ann Gastroenterol 2018;31(1):42–55. doi:10.20524/aog.2017.0209, PMID:29333066.
[6] Nakanuma Y, Sato Y, Harada K, Sasaki M, Xu J, Ikeda H. Pathological classification of intrahepatic cholangiocarcinoma based on a new concept. World J Hepatol 2010;2(12):419–427. doi:10.4254/wjh.v2.i12.419, PMID:21191517.
[7] Rimola J, Forner A, Reig M, Vilana R, de Lope CR, Ayuso C, *et al*. Cholangiocarcinoma in cirrhosis: absence of contrast washout in delayed phases by magnetic resonance imaging avoids misdiagnosis of hepatocellular carcinoma. Hepatology 2009;50(3):791–798. doi:10.1002/hep.23071, PMID:19610049.
[8] European Association for the Study of the Liver. Electronic address eee, European Association for the Study of the L. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol 2018;69(1):182–236. doi:10.1016/j.jhep.2018.03.019, PMID:29628281.
[9] Raoul JL, Forner A, Bolondi L, Cheung TT, Kloeckner R, de Baere T. Updated use of TACE for hepatocellular carcinoma treatment: How and when to use it based on clinical evidence. Cancer Treat Rev 2019;72:28–36. doi:10.1016/j.ctrv.2018.11.002, PMID:30447470.
[10] Lee AJ, Chun YS. Intrahepatic cholangiocarcinoma: the AJCC/UICC 8th edition updates. Chin Clin Oncol 2018;7(5):52. doi:10.21037/cco.2018.07.03, PMID:30180751.
[11] Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, *et al*. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med 2010;362(14):1273–1281. doi:10.1056/NEJMoa0908721, PMID:20375404.
[12] Granito A, Bolondi L. Non-transplant therapies for patients with hepatocellular carcinoma and Child-Pugh-Turcotte class B cirrhosis. Lancet Oncol 2017;18(2):e101–e112. doi:10.1016/S1470-2045(16)30569-1, PMID:28214411.
[13] Neuzillet C, Emery C, Teissier C, Bouee S, Lievre A. Patient healthcare trajectories of intrahepatic cholangiocarcinoma in France: A nationwide retrospective analysis. Lancet Reg Health Eur 2022;15:100324. doi:10.1016/j.lanepe.2022.100324, PMID:35199086.
[14] Abou-Alfa GK, Macarulla T, Javle MM, Kelley RK, Lubner SJ, Adeva J, *et al*. Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma

(ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol 2020;21(6):796–807. doi:10.1016/S1470-2045(20)30157-1, PMID:32416072.
[15] Abou-Alfa GK, Sahai V, Hollebecque A, Vaccaro G, Melisi D, Al-Rajabi R, *et al*. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. Lancet Oncol 2020;21(5):671–684. doi:10.1016/S1470-2045(20)30109-1, PMID:32203698.
[16] Javle M, Roychowdhury S, Kelley RK, Sadeghi S, Macarulla T, Weiss KH, *et al*. Infigratinib (BGJ398) in previously treated patients with advanced or metastatic cholangiocarcinoma with FGFR2 fusions or rearrangements: mature results from a multicentre, open-label, single-arm, phase 2 study. Lancet Gastroenterol Hepatol 2021;6(10):803–815. doi:10.1016/S2468-1253(21)00196-5, PMID:34358484.
[17] Oh DY, He AR, Qin S, Chen LT, Okusaka T, Vogel A, *et al*. A phase 3 randomized, double-blind, placebo-controlled study of durvalumab in combination with gemcitabine plus cisplatin (GemCis) in patients (pts) with advanced biliary tract cancer (BTC): TOPAZ-1. J Clin Oncol 2022;40(4_suppl):378–378. doi:10.1200/JCO.2022.40.4_suppl.378.
[18] Fabris L, Sato K, Alpini G, Strazzabosco M. The Tumor Microenvironment in Cholangiocarcinoma Progression. Hepatology 2021;73(Suppl 1):75–85. doi:10.1002/hep.31410, PMID:32500550.
[19] Thanee M, Loilome W, Techasen A, Namwat N, Boonmars T, Pairojkul C, *et al*. Quantitative changes in tumor-associated M2 macrophages characterize cholangiocarcinoma and their association with metastasis. Asian Pac J Cancer Prev 2015;16(7):3043–3050. doi:10.7314/apjcp.2015.16.7.3043, PMID:25854403.
[20] Darby IA, Zakuan N, Billet F, Desmouliere A. The myofibroblast, a key cell in normal and pathological tissue repair. Cell Mol Life Sci 2016;73(6):1145–1157. doi:10.1007/s00018-015-2110-0, PMID:26681260.
[21] Jesper D, Heyn SG, Schellhaas B, Pfeifer L, Goertz RS, Zopf S, *et al*. Effects of liver cirrhosis and patient condition on clinical outcomes in intrahepatic cholangiocarcinoma: a retrospective analysis of 156 cases in a single center. Eur J Gastroenterol Hepatol 2018;30(5):552–556. doi:10.1097/MEG.0000000000001036, PMID:29280922.
[22] Tovoli F, Guerra P, Iavarone M, Veronese L, Renzulli M, De Lorenzo S, *et al*. Surveillance for Hepatocellular Carcinoma Also Improves Survival of Incidentally Detected Intrahepatic Cholangiocarcinoma Arisen in Liver Cirrhosis. Liver Cancer 2020;9(6):744–755. doi:10.1159/000509059, PMID:33442543.
[23] Sagrini E, Iavarone M, Stefanini F, Tovoli F, Vavassori S, Maggioni M, *et al*. Imaging of combined hepatocellular-cholangiocarcinoma in cirrhosis and risk of false diagnosis of hepatocellular carcinoma. United European Gastroenterol J 2019;7(1):69–77. doi:10.1177/2050640618815378, PMID:30788118.
[24] Sigel CS, Drill E, Zhou Y, Basturk O, Askan G, Pak LM, *et al*. Intrahepatic Cholangiocarcinomas Have Histologically and Immunophenotypically Distinct Small and Large Duct Patterns. Am J Surg Pathol 2018;42(10):1334–1345. doi:10.1097/PAS.0000000000001118, PMID:30001234.
[25] Rizzo A, Ricci AD, Gadaleta-Caldarola G, Brandi G. Radiofrequency ablation for intrahepatic cholangiocarcinoma: a tool upon the path of integrative modalities? Expert Rev Gastroenterol Hepatol 2021;15(11):1239–1240. doi:10.1080/17474124.2021.1974296, PMID:34449276.
[26] Fujimoto A, Furuta M, Shiraishi Y, Gotoh K, Kawakami Y, Arihiro K, *et al*. Whole-genome mutational landscape of liver cancers displaying biliary phenotype reveals hepatitis impact and molecular diversity. Nat Commun 2015;6:6120. doi:10.1038/ncomms7120, PMID:25636086.
[27] Hill MA, Alexander WB, Guo B, Kato Y, Patra K, O'Dell MR, *et al*. Kras and Tp53 Mutations Cause Cholangiocyte- and Hepatocyte-Derived Cholangiocarcinoma. Cancer Res 2018;78(16):4445–4451. doi:10.1158/0008-5472.CAN-17-1123, PMID:29871934.
[28] Sekiya S, Suzuki A. Intrahepatic cholangiocarcinoma can arise from Notch-mediated conversion of hepatocytes. J Clin Invest 2012;122(11):3914–3918. doi:10.1172/JCI63065, PMID:23023701.
[29] Seok JY, Na DC, Woo HG, Roncalli M, Kwon SM, Yoo JE, *et al*. A fibrous stromal component in hepatocellular carcinoma reveals a cholangiocarcinoma-like gene expression trait and epithelial-mesenchymal transition. Hepatology 2012;55(6):1776–1786. doi:10.1002/hep.25570, PMID:22234953.
[30] Estes C, Anstee QM, Arias-Loste MT, Bantel H, Bellentani S, Caballeria J, *et al*. Modeling NAFLD disease burden in China, France, Germany, Italy, Japan, Spain, United Kingdom, and United States for the period 2016-2030. J Hepatol 2018;69(4):896–904. doi:10.1016/j.jhep.2018.05.036, PMID:29886156.
[31] Zen C, Zen Y, Mitry RR, Corbeil D, Karbanova J, O'Grady J, *et al*. Mixed phenotype hepatocellular carcinoma after transarterial chemoembolization and liver transplantation. Liver Transpl 2011;17(8):943–954. doi:10.1002/lt.22314, PMID:21491582.
[32] Gautheron J, Gores GJ, Rodrigues CMP. Lytic cell death in metabolic liver disease. J Hepatol 2020;73(2):394–408. doi:10.1016/j.jhep.2020.04.001, PMID:32298766.
[33] Seehawer M, Heinzmann F, D'Artista L, Harbig J, Roux PF, Hoenicke L, *et al*. Necroptosis microenvironment directs lineage commitment in liver cancer. Nature 2018;562(7725):69–75. doi:10.1038/s41586-018-0519-y, PMID:30209397.
[34] Vitale A, Trevisani F, Farinati F, Cillo U. Treatment of Hepatocellular Carcinoma in the Precision Medicine Era: From Treatment Stage Migration to Therapeutic Hierarchy. Hepatology 2020;72(6):2206–2218. doi:10.1002/hep.31187, PMID:32064645.
[35] Reig M, Forner A, Rimola J, Ferrer-Fabrega J, Burrel M, Garcia-Criado A, *et al*. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. J Hepatol 2022;76(3):681–693. doi:10.1016/j.jhep.2021.11.018, PMID:34801630.
[36] Pelizzaro F, Penzo B, Peserico G, Imondi A, Sartori A, Vitale A, *et al*. Monofocal hepatocellular carcinoma: How much does size matter? Liver Int 2021;41(2):396–407. doi:10.1111/liv.14718, PMID:33155401.
[37] Hajiev S, Allara E, Motedayen Aval L, Arizumi T, Bettinger D, Pirisi M, *et al*. Impact of age on sorafenib outcomes in hepatocellular carcinoma: an international cohort study. Br J Cancer 2021;124(2):407–413. doi:10.1038/s41416-020-01116-9, PMID:33071284.
[38] Raoul JL, Adhoute X, Penaranda G, Perrier H, Castellani P, Oules V, *et al*. Sorafenib: Experience and Better Manage-ment of Side Effects Improve Overall Survival in Hepatocellular Carcinoma Patients: A Real-Life Retrospective Analysis. Liver Cancer 2019;8(6):457–467. doi:10.1159/000497161, PMID:31799203.
[39] Kirstein MM, Scheiner B, Marwede T, Wolf C, Voigtlander T, Semmler G, *et al*. Sequential systemic treatment in patients with hepatocellular carcinoma. Aliment Pharmacol Ther 2020;52(1):205–212. doi:10.1111/apt.15789, PMID:32432799.
[40] Uchikawa S, Kawaoka T, Aikata H, Kodama K, Nishida Y, Inagaki Y, *et al*. Clinical outcomes of sorafenib treatment failure for advanced hepatocellular carcinoma and candidates for regorafenib treatment in real-world practice. Hepatol Res 2018;48(10):814–820. doi:10.1111/hepr.13180, PMID:29682855.
[41] Yoon JG, Kim MH, Jang M, Kim H, Hwang HK, Kang CM, *et al*. Molecular Characterization of Biliary Tract Cancer Predicts Chemotherapy and Programmed Death 1/Programmed Death-Ligand 1 Blockade Responses. Hepatology 2021;74(4):1914–1931. doi:10.1002/hep.31862, PMID:33884649.
[42] Phelip JM, Desrame J, Edeline J, Barbier E, Terrebonne E, Michel P, *et al*. Modified FOLFIRINOX Versus CISGEM Chemotherapy for Patients With Advanced Biliary Tract Cancer (PRODIGE 38 AMEBICA): A Randomized Phase II Study. J Clin Oncol 2022;40(3):262–271. doi:10.1200/JCO.21.00679, PMID:34662180.
[43] Mateo J, Chakravarty D, Dienstmann R, Jezdic S, Gonzalez-Perez A, Lopez-Bigas N, *et al*. A framework to rank genomic alterations as targets for cancer precision medicine: the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT). Ann Oncol 2018;29(9):1895–1902. doi:10.1093/annonc/mdy263, PMID:30137196.
[44] Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, *et al*. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med 2020;382(20):1894–1905. doi:10.1056/NEJMoa1915745, PMID:32402160.