Surgery xxx (2023) 1–11

Contents lists available at ScienceDirect

Surgery

journal homepage: www.elsevier.com/locate/surg

Combined hepatocellular-cholangiocarcinoma compared to hepatocellular carcinoma and intrahepatic cholangiocarcinoma: Different survival, similar recurrence
Report of a large study on repurposed databases with propensity score matching

Boris Amory, MD[a], Claire Goumard, MD, PhD[b], Alexis Laurent, MD, PhD[c], Serena Langella, MD[d], Daniel Cherqui, MD, PhD[e], Ephrem Salame, MD, PhD[f], Louise Barbier, MD, PhD[f], Olivier Soubrane, MD[g], Olivier Farges, MD, PhD[h], Christian Hobeika, MD[h], Takayuki Kawai, MD, PhD[i], Jean-Marc Regimbeau, MD, PhD[j], François Faitot, MD, PhD[k], Patrick Pessaux, MD, PhD[l], Stéphanie Truant, MD, PhD[m], Emmanuel Boleslawski, MD, PhD[m], Astrid Herrero, MD, PhD[n], Jean-Yves Mabrut, MD[o], Laurence Chiche, MD[p], Marcello Di Martino, MD[q], Rami Rhaiem, MD[r], Lilian Schwarz, MD, PhD[s], Vivian Resende, MD, PhD[t], Julien Calderaro, MD, PhD[u], Jérémy Augustin, MD, PhD[u], Stefano Caruso, MD, PhD[u], Daniele Sommacale, MD[v], Stefan Hofmeyr, MD[w], Alessandro Ferrero, MD[d], David Fuks, MD, PhD[x], Eric Vibert, MD, PhD[e], Guido Torzilli, MD, PhD[y], Olivier Scatton, MD, PhD[b], Raffaele Brustia, MD, PhD[z,*], on behalf of the AFC-ICC-2009, AFC-LLR-2018, and PRS-2019 Study Group

[a] *Department of Digestive and Hepato-pancreatic-biliary Surgery, AP-HP, Hôpital Henri-Mondor, Paris Est Créteil University, UPEC, France; Assistance Publique-Hôpitaux de Paris, Créteil, France*
[b] *Department of Hepatobiliary and Liver Transplantation Surgery, AP-HP, Hôpital Pitié Salpètrière, CRSA, Sorbonne Université, Paris, France*
[c] *Department of Digestive and Hepato-pancreatic-biliary Surgery, DMU CARE, Assistance Publique-Hôpitaux de Paris (AP-HP), Hôpitaux Universitaires Henri Mondor, Créteil, France; Paris Est Créteil University, UPEC, France; Team "Pathophysiology and Therapy of Chronic Viral Hepatitis and Related Cancers," INSERM U955, Créteil, France; Assistance Publique-Hôpitaux de Paris, Créteil, France*
[d] *Department of General and Oncological Surgery, Ospedale Mauriziano, Torino, Italy*
[e] *Center Hepato-Biliaire, AP-HP Paul Brousse Hospital, Paris-Saclay University, Villejuif, France*
[f] *Department of Digestive Surgery and Liver Transplantation, University Hospital of Tours, University of Tours, France; FHU Support, Tours, France*
[g] *Department of Digestive, Oncological, and Metabolic Surgery, Institut Mutualiste Montsouris, Paris, France*
[h] *Department of HPB Surgery and Liver Transplantation, AP-HP Beaujon Hospital, University of Paris, Clichy, France*
[i] *Department of Surgery, Medical Research Institute, Kitano Hospital, Osaka and Graduate School of Medicine, Kyoto University, Japan*
[j] *SSPC (Simplification of Surgical Patients Care) - Clinical Research Unit, University of Picardie Jules Verne, Amiens, France; Department of Digestive Surgery, Amiens University Medical Center, France*
[k] *Service de Chirurgie Hépato-Biliaire et Transplantation Hépatique, Hôpital de Hautepierre, Strasbourg, France*
[l] *Unité Chirurgie HBP, Pôle hépato-digestif Nouvel Hôpital Civil, Strasbourg, France; Institut of Viral and Liver Disease, Inserm U1110, Strasbourg, France*
[m] *Department of Digestive Surgery and Transplantation, University Hospitals, Lille, France*
[n] *Department of HBP Surgery and Liver Transplantation, Montpellier University Hospital, University of Montpellier, France*
[o] *Croix Rousse University Hospital, Department of General Surgery and Liver Transplantation, Lyon, France; Cancer Research Center of Lyon, INSERM U1052, France*
[p] *Department of Hepato-Bilio-Pancreatic Surgery and Liver Transplantation, Haut Lévêque Hospital, Center Hospitalier Universitaire de Bordeaux, France; Inserm UMR 1312-Team 3 "Liver Cancers and Tumoral Invasion," Bordeaux Institute of Oncology, University of Bordeaux, France*
[q] *HPB Unit, Department of General and Digestive Surgery, Hospital Universitario de la Princesa, Instituto de Investigación Sanitaria Princesa (IIS-IP), Universidad Autónoma de Madrid (UAM), Madrid, Spain*
[r] *Department of Hepatobiliary, Pancreatic, and Digestive Surgery, Robert Debré University Hospital, Reims, France; University Reims Champagne-Ardenne, France*
[s] *Department of Genomic and Personalized Medicine in Cancer and Neurological Disorders, Rouen University Hospital, UNIROUEN, UMR 1245 INSERM, Normandie Rouen University, France*
[t] *Federal University of Minas Gerais School of Medicine, Belo Horizonte, Brazil*
[u] *Université Paris Est Créteil, INSERM, IMRB, Créteil, France; Assistance Publique-Hôpitaux de Paris, Henri Mondor-Albert Chenevier University Hospital, Department of Pathology, Créteil, France; Inserm, U955, Team 18, Créteil, France*
[v] *Department of Digestive and Hepato-pancreatic-biliary Surgery, DMU CARE, Assistance Publique-Hôpitaux de Paris (AP-HP), Hôpitaux Universitaires Henri Mondor, Créteil, France; Paris Est Créteil University, UPEC, Créteil, France; Team "Pathophysiology and Therapy of Chronic Viral Hepatitis and Related*

https://doi.org/10.1016/j.surg.2023.09.040

Cancers," INSERM U955, Créteil, France; Assistance Publique-Hôpitaux de Paris, Créteil, France
[w] Division of Surgery, Faculty of Medicine and Health Sciences, Stellenbosch University and Tygerberg Academic Hospital, Cape Town, South Africa
[x] Department of Hepato-Pancreatic-Biliary and Endocrine Surgery, Hopital Cochin, Assistance Publique-Hôpitaux de Paris, France; Université Paris Cité, France
[y] Division of Hepatobiliary and General Surgery, Department of Surgery, Humanitas Research Hospital - IRCCS, Humanitas University, Rozzano, Milan, Italy
[z] Department of Digestive and Hepato-pancreatic-biliary Surgery, DMU CARE, Assistance Publique-Hôpitaux de Paris (AP-HP), Hôpitaux Universitaires Henri Mondor, Créteil, France; Paris Est Créteil University, UPEC, France; Team "Pathophysiology and Therapy of Chronic Viral Hepatitis and Related Cancers," INSERM U955, Créteil, France; Assistance Publique-Hôpitaux de Paris, Créteil, France

ARTICLE INFO

Article history:
Accepted 26 September 2023
Available online xxx

ABSTRACT

Background: Combined hepatocholangiocarcinoma is a rare cancer with a grim prognosis composed of both hepatocellular carcinoma and intrahepatic cholangiocarcinoma morphologic patterns in the same tumor. The aim of this multicenter, international cohort study was to compare the oncologic outcomes after surgery of combined hepatocholangiocarcinoma to hepatocellular carcinoma and intrahepatic cholangiocarcinoma.
Methods: Patients treated by surgery for combined hepatocholangiocarcinoma, hepatocellular carcinoma, and intrahepatic cholangiocarcinoma from 2000 to 2021 from multicenter international databases were analyzed retrospectively. Patients with combined hepatocholangiocarcinoma (cases) were compared with 2 control groups of hepatocellular carcinoma or intrahepatic cholangiocarcinoma, sequentially matched using a propensity score based on 8 preoperative characteristics. Overall and disease-free survival were compared, and predictors of mortality and recurrence were analyzed with Cox regression after propensity score matching.
Results: During the study period, 3,196 patients were included. Propensity score adjustment and 2 sequential matching processes produced a new cohort ($n = 244$) comprising 3 balanced groups was obtained (combined hepatocholangiocarcinoma = 56, intrahepatic cholangiocarcinoma = 66, and hepatocellular carcinoma = 122). Kaplan–Meier overall survival estimations at 1, 3, and 5 years were 67%, 45%, and 28% for combined hepatocholangiocarcinoma, 92%, 75%, and 55% for hepatocellular carcinoma, and 86%, 53%, and 42% for the intrahepatic cholangiocarcinoma group, respectively ($P = .0014$). Estimations of disease-free survival at 1, 3, and 5 years were 51%, 25%, and 17% for combined hepatocholangiocarcinoma, 63%, 35%, and 26% for the hepatocellular carcinoma group, and 51%, 31%, and 28% for the intrahepatic cholangiocarcinoma group, respectively ($P = .19$). Predictors of mortality were combined hepatocholangiocarcinoma subtype, metabolic syndrome, preoperative tumor markers alpha-fetoprotein and carbohydrate antigen 19-9, and satellite nodules, and recurrence was associated with satellite nodules rather than cancer subtype.
Conclusion: Despite data limitations, overall survival among patients with combined hepatocholangiocarcinoma was worse than both groups and closer intrahepatic cholangiocarcinoma, whereas disease-free survival was similar among the 3 groups. Future research on immunophenotypic profiling may hold more promise than traditional nonmodifiable clinical characteristics (as found in this study) in predicting recurrence or response to salvage treatments.

Introduction

Primary liver cancer (PLC) is the third most common cause of cancer-related deaths worldwide, consisting mainly of hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCA), accounting, respectively, for 85% and 10% of all PLCs,[1,2] respectively. Combined hepatocholangiocarcinoma (cHCC-CCA), is histopathologically characterized by the presence of both HCC and intrahepatic CCA (iCCA) morphologic patterns in the same lesion. With an incidence of 0.05/100,000 in the general population, cHCC-CCAs represents nearly 1% to 4% of all PLCs.[2–4]

The combination of low cHCC-CCA incidence, overlapping phenotypes, single-center series, challenging preoperative diagnosis, and poor knowledge of the immune microenvironment may explain the poor observed prognosis, which is similar to iCCA and worse than HCC.[3,5,6]

The aim of this multicenter, international cohort study was to compare the oncologic outcomes after surgery of patients affected by cHCC-CCA to those affected by HCC and iCCA.

Methods

This study was designed as an international, multicenter cohort study to compare the oncologic outcomes of liver

Collaborators
AFC-ICC-2009, AFC-LLR-2018, and PRS-2019 Study Group:
Julio Abba, René Adam, Mustapha Adham, Pietro Addeo, Marc-Antoine Allard, Giuliana Amaddeo, Ahmet Ayav, Daniel Azoulay, Philippe Bachellier, Pierre Balladur, Julien Barbieux, Karim Boudjema, M Bougard, Emmanuel Buc, Petru Bucur, Antoine Carmelo, François Cauchy, Denis Chatelain, Jean Chauvat, Zineb Cherkaoui, Mircea Chirica, Oriana Ciacio, Tatiana Codjia, Fabio Colli, Luciano De Carlis, Jean-Robert Delpero, Nicolas Demartines, Olivier Detry, Marcelo Dias Sanches, Momar Diouf, Alexandre Doussot, Christian Ducerf, Mehdi El Amrani, Jacques Ewald, Jean-Marc Fabre, Hervé Fagot, Simone Famularo, Léo Ferre, Francesco Fleres, Gilton Marques Fonseca, Álvaro Gancedo Quintana, Brice Gayet, Alessandro Giacomoni, Jean-Francois Gigot, Nicolas Golse, Emilie Gregoire, Jean Hardwigsen, Paulo Herman, Thevi Hor, François Jehaes, Ali-Reza Kianmanesh, Shohei Komatsu, Sophie Laroche, Christophe Laurent, Yves-Patrice Le Treut, Philippe Leourier, Emilie Lermite, Mikael Lesurtel, Christian Letoublon, Paul Leyman, Jean Lubrano, Jean-Yves Mabrut, Georges Mantion, Ugo Marchese, Elena Martín-Pérez, Benjamin Menahem, Maxime Meunier, Guillaume Millet, Kayvan Mohkam, André Mulliri, Fabrice Muscari, Francis Navarro, Francisco Nolasco, Takeo Nomi, Jean Nunoz, Gennaro Nuzzo, Shinya Okumura, Nassima Oudafal, Gerard Pascal, Guillaume Passot, Damiano Patrono, François Paye, Fabiano Perdigao, Niccolo Petrucciani, Gabriella Pittau, François-René Pruvot, Artigas Raventos, Hélène Regnault, Michel Rivoire, Renato Romagnoli, Didier Roulin, Antonio Sa-Cunha, Michel Scotte, François-Regis Souche, Bertrand Suc, Alexandre Thobie, Boris Trechot, Olivier Turini, Shinji Uemoto, Xavier Unterteiner, Charles Vanbrugghe, Jean Zemour.

* Reprint requests: Raffaele Brustia, MD, PhD, Department of HPB and Digestive Surgery, Service de Chirurgie digestive et Hépato-bilio-pancréatique, GHU AP-HP Hôpitaux Universitaires Henri-Mondor, 51, avenue du Maréchal de Lattre de Tassigny, 94010 Créteil Cedex, France.
E-mail address: raffaele.brustia@aphp.fr (R. Brustia).

resection (LR) within the target population of patients affected by cHCC-CCA.

Patients with cHCC-CCA were considered to be cases, and compared with 2 control groups represented by patients with HCC or iCCA, matched through a propensity score (PS) based on preoperative characteristics.

This study was designed in November 2021 in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement.[7]

Participants and study size

Given the low incidence of the disease, even in referral centers, data from 3 cohorts and 1 independent multicenter database were explored for eligibility, extracted and merged. The study period assessed was from 2000 to 2021, with at least 6 months of follow-up. Based on the retrospective nature of the study and repurposing existing databases, no ethical committee or institutional review board approval was needed.

Data sources

1) Cohorts
   - French cohort AFC-ICC-2009 composed of patients treated for cholangiocarcinoma[8] (sample $n = 726$).
   - French cohort AFC-LLR-2018 for laparoscopic liver surgery (sample $n = 4,215$).
   - A multicenter international cohort[9] of patients affected by iCCA, assembled to explore a preoperative risk score (PRS_2019) (sample $n = 355$).
2) Multicenter database
   - Seven academic referral centers from France (GHU Henri Mondor, Creteil; Pitié Salpêtrière Hospital, Paris; CHU Montpellier, Montpellier), Italy (Ospedale Mauriziano, Torino; Istituto Humanitas, Milan), Spain (La Princesa Hospital, Spain), and South Africa (Tygerberg Academic Hospital, Cape Town) shared individual patient data treated by LR for cHCC-CCA, iCCA, or HCC (sample $n = 923$).

Patients were further screened according to the following inclusion criteria:

- Patients underwent LR with curative intent (R0 or R1).
- The pattern of cHCC-CCA, HCC, or CC was histopathologically confirmed (gallbladder cancer, cystadenocarcinomas, and hilar cholangiocarcinomas were excluded).

Patients from each database were screened for duplicates and data completeness, and then sequentially merged into a raw database including $n = 3,196$ patients, which represented the unmatched study cohort. A preliminary analysis to inspect the effect of the long inclusion period was carried out, by comparing the decades 2000 to 2010 and 2011 to 2021.

Patient selection

1) Cases

cHCC-CCA

Data were sourced from the cohort of patients affected by cHCC-CCA nested in the French AFC-LLR-2018 study group for laparoscopic surgery, as well as individual patient data from 6 out of the 7 centers contributing to the multicenter database (GHU Henri Mondor, Creteil; CHU Montpellier, Montpellier; Ospedale Mauriziano, Torino; Istituto Humanitas, Milan; Tygerberg Academic Hospital, Cape Town). The cumulative sample amounted to 131 patients affected by cHCC-CCA.

2) Controls

a. iCCA

Data source for this control group were extracted from 2 national French cohorts (AFC-ICC-2009 of patients treated for cholangiocarcinoma[8] and the nested cohort of patients with iCCA within the AFC-LLR-2018 study group on laparoscopic surgery), as well as a third supplementary multicenter international cohort[9] focusing on a preoperative risk score in iCCA patients. The cumulative sample included 1,070 patients affected by iCCA.

b. HCC

Data were included from the subgroup of patients with HCC contained in the French AFC-LLR-2018 study group for laparoscopic surgery, and individual patient data from 3 out of the 7 centers participating in the multicenter database (Mauriziano Hospital, La Princesa Hospital, Spain, Pitié Salpêtrière Hospital, France). The cumulative sample included 1,995 patients affected by HCC.

Propensity score matching

To achieve a well-balanced data frame of the 3 groups, and in the absence of dedicated and widely accepted methods for 1:1:1 matching, patients were sequentially matched by a 2-step process to achieve balance between the data of the 3 cohorts, as described in the statistical analysis methods paragraph and represented in Figure 1.

Variables

Preoperative variables reported in each database were merged in a single data set for analysis and included age, sex, underlying liver disease, ASA classification, alpha-fetoprotein (AFP), and carbohydrate antigen 19-9 (CA19-9) levels.

The extent of LR was considered major when involving more than 3 segments, and further classified according to the Institut Mutualiste Montsouris (IMM) Difficulty classification,[10] describing 3 increasing levels of difficulty according to the number, and location of resected liver segments. A similar 3-level classification applies to open surgery,[11] and for the sake of simplicity, the variable labeled “IMM difficulty classification” was used for both minimally invasive and open hepatectomy. Pathological data on tumors were examined, including size, number, grade, satellite lesions, vascular invasion, surgical margin, and nodes when available (since data were sourced from more than 60 centers, the investigators had no access to individual patient data and seldom to the number of nodes retrieved). For the same reasons, preoperative biology and CHILD or MELD scores were not available.

Hospital stay was defined as the time spent in hospital during the primary admission from day of operation to discharge.

Complications were described according to the Clavien-Dindo classification[12] and collected within 90 days after surgery. Complications were designated severe if more or equal to ($\geq$) grade III, including postoperative death.

Each case was anonymized and assigned a unique alphanumeric code.

The data set worksheet was hosted on a secure computer with limited access and password protection. Data management was compliant with the reference methodology on personal data processing and protection (MR003 and MR004), as dictated by the

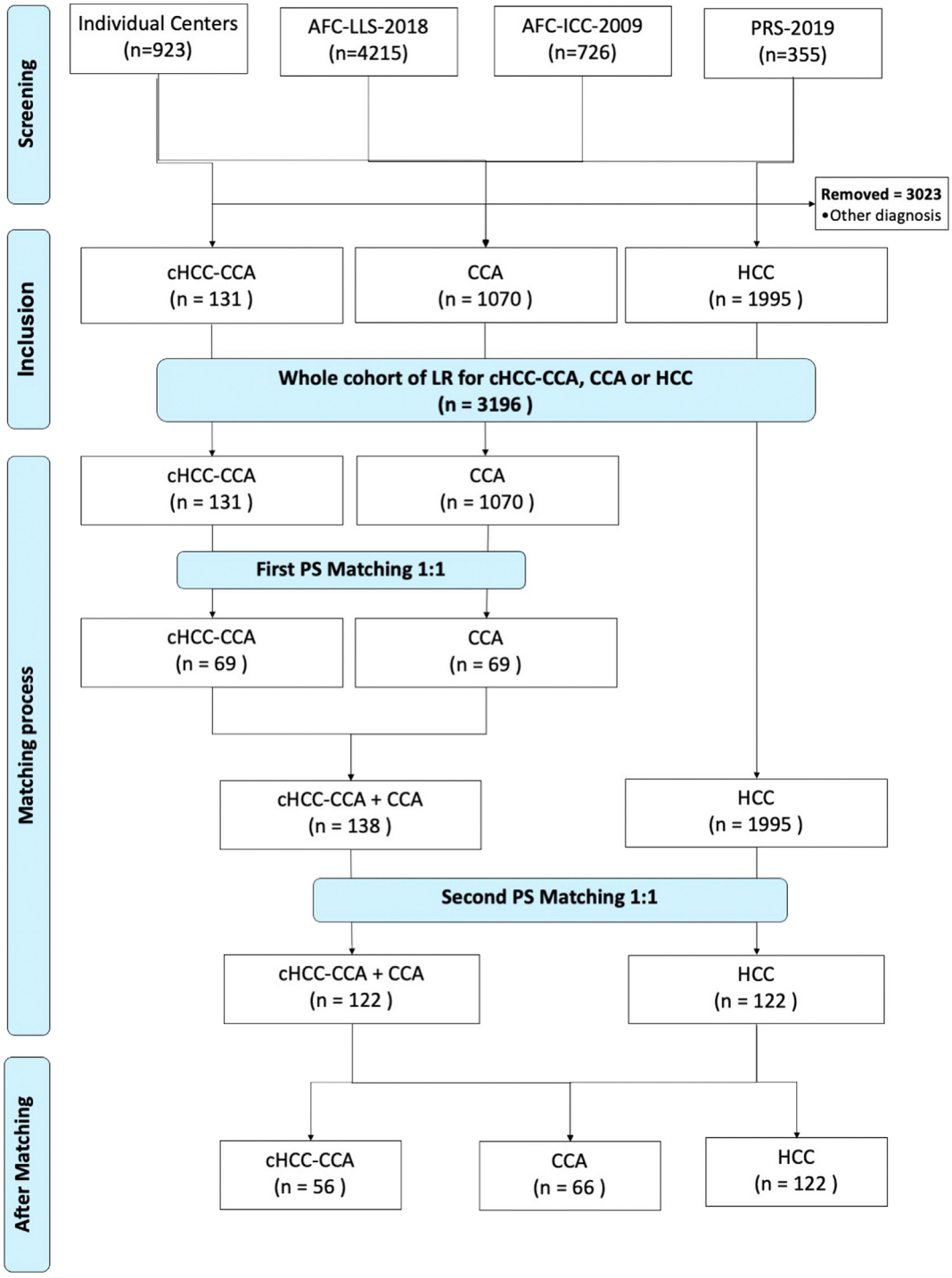

Figure 1. Flowchart of the patients included in the cohort.

French data protection authority (Commission Nationale de l'Informatique et des Libertés).

Study objectives

The primary objective was to compare overall survival (OS) between patients operated for cHCC-CCA, iCCA, and HCC after propensity score matching. Variables required to measure the primary endpoint were the event (death) and time until the event (OS), the latter defined as the time from surgery to death or last follow-up.

Secondary objectives were to compare disease-free survival (DFS) between the 3 groups after PS matching, as well as risk factors for mortality or recurrence.

Statistical analysis methods

Statistical software

Data management and statistical analysis were performed with R software (version 4.1.2 or higher; R Foundation for Statistical Computing. www.cran.r-project.org, Vienna, Austria). All the packages, libraries, and functions refer to the R software.

Descriptive statistics

Categorical variables were reported as percentages, whereas continuous variables were summarized as means and standard deviation (SD) or median and range for discrete variables, as appropriate. The Student's *t* test or Mann-Whitney *U* test were used for comparisons of quantitative variables as appropriate, whereas a χ^2 test or Fisher's exact test were used to compare categorical data. Data were compared before and after matching. In case of data visualization, the ggplot2 package was used.

Propensity score matching

Potential prognostic biases due to the different distribution of covariates among patients affected by cHCC-CCA, iCCA, or HCC were controlled by 2 sequential matching steps (Figure 1). Each step allowed pair matching on the basis of a propensity score (MatchIt package), which included 8 preoperative covariates: sex (M/F), patient's age (<50 years, ≤ 50 years, <70 years, ≥ 70 years), ASA class (I to IV), BMI >30 kg/m^2 (Y/N), cirrhosis, difficulty classification (IMM classification, as defined above[10,11]), number of lesions (single/multiple), and tumor size (<30 mm, ≤ 30 mm <50 mm, ≥ 50 mm).

The sequential matching process was performed twice.

- First PS matching: cHCC-CCA (n = 131, cases) patients were matched with the control group of iCCA (n = 1,070), without replacement (1:1 ratio), to minimize conditional bias. For each patient with cHCC-CCA, a nearest score neighbor affected by iCCA was matched. Multiple caliper widths were tested. A caliper width of 0.02 resulted in the best tradeoff between homogeneity and retained sample size (n = 138) with 2 well-balanced groups of patients affected by cHCC-CCA (n = 69) and iCCA (n = 69).
- Second PS matching: the same process was used to compare each patient in the cHCC-CCA+iCCA group (new cases: n = 138, cHCC-CCA and iCCA) with the control group of HCC (n = 1,995), without replacement (1:1 ratio), through a new PS based on the same preoperative characteristics.

These 2 steps generated a new data set (n = 244), which represented the final study cohort, with 3 balanced groups of patients affected by cHCC-CCA (n = 56), iCCA (n = 66), and HCC (n = 122), which were compared with respect to propensity score.

Survival analyses

Kaplan–Meier curves for OS and DFS before and after matching were created through survfit and ggsurvplot functions from survminer and survival packages, with 3 strata corresponding to cHCC-CCA, iCCA, or HCC groups.

Definition of variables predicting death or recurrence within the whole cohort.

Unadjusted hazard ratios (HRs) and 95% confidence intervals (95% CI) were calculated by Cox proportional hazards regression analysis for perioperative variables associated with death or recurrence. Variables with a *P* value <.1 (as well as those considered clinically relevant) were entered in a multivariate Cox model to identify factors independently associated with death or recurrence. The final model expressed the adjusted HRs and 95% CI.

Missing data

The 79 variables included in the final data set were inspected with the vis_miss function of the visdat package. After exclusion of 8 variables with a missing rate >80%, the whole database was 91.6% complete (missing data = 8.4%). Noteworthy underlying liver disease (HBV, HCV, NASH), length of stay, blood loss, transfusion, tumoral thrombosis, T and N status were missing. No imputation methods were used to replace missing variables.

Results

Participants

A total of 3,196 patients undergoing surgery for cHCC-CCA (n = 131, 4.1%), iCCA (n = 1,070, 33.5%), and HCC (n = 1,995, 62.4%) from more than 50 participating centers were included during the study period (2000–2021) and represented the study cohort (Figure 1). Among them, 69.5% (n = 2,220) were male. The cohort had a median BMI of 26.3 ± 4.8 kg/m^2 and was affected by metabolic syndrome in 31.9% (n = 509) of cases. Cirrhosis was observed in 50.7% (n = 1,413) of patients. According to the IMM difficulty classification of liver resection, 42.9% (n = 1,266), 21.0% (n = 619), and 36.1% (n = 1,066) were graded I, II, and III, respectively (P < .001). Within the whole cohort and during the follow-up period (24.3 ± 26.4 months), 28.5% of patients experienced death (n = 814) and 47.0% recurrence (n = 1,364). More details are reported in Table I.

When focusing on the subgroup of patients affected by cHCC-CCA, 78.6% were males (n = 103) with a mean age of 61.9 ± 11.5 years, and cirrhosis was observed in 51.1% (n = 67) of them. The tumor diameter was >50 mm in 42% of patients (n = 55), with multiple lesions in 25.6% of cases (n = 33) and the presence of satellite nodules observed in 51.3% of patients (n = 61). Preoperative tumoral markers were AFP 4,606.1 ± 19,225.7 ng/mL and CA 19-9 782.2 ± 5,498.6 U/mL.

Propensity score model

After propensity score adjustment and sequential matching the demographic and preoperative variables of patients (n = 244) (cHCC-CCA = 56, iCCA = 66, and HCC =122) were similar (Table I), except for the presence of metabolic syndrome (cHCC-CCA 44.6% n = 25, HCC 24.6% n = 30 and iCCA 33.3% n = 22; P = .002), preoperative CA 19-9 (cHCC-CCA = 140.72 ± 336.33, HCC = 11.46 ± 10.11, and iCCA = 6,410.20 ± 15,998.25; P = .042) and the need for PVE (cHCC-CCA 8.9% n = 5, HCC 2.5% n = 3, and iCCA 4.5% n = 3; P = .047). Given the long study interval, the historical distribution (secular trend) was explored. A higher rate of patients was treated in the second decade (2011–2021) compared to the previous one (2000–2010) with 73.8% (n = 180) of patients distributed as follows: cHCC-CCA 75% (n = 42), HCC 80.3% (n = 98), and iCCA 60.6% (n = 40). Hence, no survival differences (overall and disease free) were observed between the 2 inclusions periods (Supplementary Figures S1 and S2).

Overall survival, before and after matching

Within the whole cohort of 3,162 patients, 81.5% (n = 2,602) were analyzed (n = 594 patients excluded because of incomplete data). Kaplan–Meier OS estimations at 1, 3, and 5 years were 71%, 43%, and 28% for cHCC-CCA; 91%, 79%, and 68% for the HCC group; and 84%, 55%, and 41% for the iCCA group, respectively (P < .001) (Figure 2).

After matching, Kaplan–Meier OS estimations at 1, 3, and 5 years were 67%, 45%, and 28% for cHCC-CCA; 92%, 75%, and 55% for the HCC group; and 86%, 53%, and 42% for the iCCA group, respectively (P = .0014) (Figure 3).

Table I
Clinical characteristics of the cohort, before and after matching.

	Unmatched cohort				*P*	Matched cohort				*P*
	Overall	cHCC-CCA	HCC	CCA		Overall	cHCC-CCA	HCC	CCA	
n	3196	131	1995	1070		244	56	122	66	
Liver cancer (%)					<0.001					<0.001
cHCC-CCA	131 (4.1)	131 (100.0)	0 (0.0)	0 (0.0)		56 (23.0)	56 (100.0)	0 (0.0)	0 (0.0)	
HCC	1995 (62.4)	0 (0.0)	1995 (100.0)	0 (0.0)		122 (50.0)	0 (0.0)	122 (100.0)	0 (0.0)	
CCA	1070 (33.5)	0 (0.0)	0 (0.0)	1070 (100.0)		66 (27.0)	0 (0.0)	0 (0.0)	66 (100.0)	
Sex = M (%)*	2220 (69.5)	103 (78.6)	1568 (78.6)	549 (51.3)	<0.001	180 (73.8)	42 (75.0)	92 (75.4)	46 (69.7)	0.677
Age (mean (SD))	65.02 (12.23)	61.89 (11.47)	65.29 (12.49)	64.91 (11.77)	0.008	65.13 (10.96)	64.91 (10.79)	65.79 (11.21)	64.09 (10.70)	0.592
Age, class (%)*					0.045					0.918
<50 y	327 (10.4)	16 (12.2)	194 (9.8)	117 (11.2)		18 (7.4)	4 (7.1)	8 (6.6)	6 (9.1)	
50-70 y	1,755 (55.6)	85 (64.9)	1,111 (56.0)	559 (53.7)		151 (61.9)	33 (58.9)	76 (62.3)	42 (63.6)	
>70 y	1,074 (34.0)	30 (22.9)	679 (34.2)	365 (35.1)		75 (30.7)	19 (33.9)	38 (31.1)	18 (27.3)	
BMI (mean (SD))	26.29 (4.83)	25.89 (4.60)	26.53 (4.82)	25.80 (4.84)	0.002	27.23 (4.65)	26.81 (4.82)	26.83 (4.59)	28.32 (4.51)	0.088
BMI >30 kg/m^2 (%)*	509 (20.2)	25 (19.5)	355 (21.0)	129 (18.6)	0.416	64 (26.2)	14 (25.0)	29 (23.8)	21 (31.8)	0.475
Metabolic syndrome (%)	669 (31.9)	45 (35.2)	459 (33.2)	165 (28.0)	0.051	77 (31.6)	25 (44.6)	30 (24.6)	22 (33.3)	0.002
ASA (%)*					<0.001					0.818
I	234 (10.5)	10 (7.8)	152 (10.4)	72 (11.1)		18 (7.4)	3 (5.4)	10 (8.2)	5 (7.6)	
II	1045 (46.8)	70 (54.7)	613 (42.1)	362 (56.0)		125 (51.2)	26 (46.4)	62 (50.8)	37 (56.1)	
III	889 (39.8)	43 (33.6)	650 (44.6)	196 (30.3)		99 (40.6)	26 (46.4)	49 (40.2)	24 (36.4)	
IV	64 (2.9)	5 (3.9)	42 (2.9)	17 (2.6)		2 (0.8)	1 (1.8)	1 (0.8)	0 (0.0)	
Cirrhosis = 1 (%)	1413 (50.7)	67 (51.1)	1141 (64.9)	205 (22.8)	<0.001	87 (35.7)	24 (42.9)	43 (35.2)	20 (30.3)	0.350
TACE = 1 (%)	188 (11.1)	17 (13.5)	171 (12.0)	0 (0.0)	<0.001	13 (5.3)	7 (12.5)	6 (4.9)	0 (0.0)	<0.001
PVE = 1 (%)	194 (7.3)	13 (10.2)	121 (7.4)	60 (6.6)	0.326	11 (4.5)	5 (8.9)	3 (2.5)	3 (4.5)	0.047
Preoperative AFP (mean (SD))	2589.89 (19413.68)	4606.07 (19225.67)	2407.83 (19975.61)	16.94 (53.65)	0.397	3499.94 (17606.04)	8104.93 (28366.06)	895.94 (3269.40)	9.44 (12.55)	0.096
Preoperative CA19-9 (mean (SD))	991.20 (5885.17)	782.22 (5498.58)	13.39 (23.51)	1723.81 (7641.87)	0.092	2359.50 (9926.73)	140.72 (336.33)	11.46 (10.11)	6410.20 (15998.25)	0.042
IMM (%)*					<0.001					0.576
I	1266 (42.9)	107 (82.9)	953 (51.5)	206 (21.2)		170 (69.7)	35 (62.5)	85 (69.7)	50 (75.8)	
II	619 (21.0)	10 (7.8)	412 (22.2)	197 (20.3)		32 (13.1)	10 (17.9)	16 (13.1)	6 (9.1)	
III	1066 (36.1)	12 (9.3)	487 (26.3)	567 (58.5)		42 (17.2)	11 (19.6)	21 (17.2)	10 (15.2)	
Major hepatectomy (%)	1139 (36.1)	13 (9.9)	397 (20.0)	729 (69.9)	<0.001	53 (21.7)	13 (23.2)	24 (19.7)	16 (24.2)	0.733
Open vs Lap (Open) (%)	1125 (35.3)	31 (23.7)	308 (15.5)	786 (73.5)	<0.001	68 (27.9)	14 (25.0)	30 (24.6)	24 (36.4)	0.197
Clavien-Dindo ≥III 90d (%)	225 (12.6)	28 (21.4)	159 (10.5)	38 (27.3)	<0.001	34 (13.9)	12 (21.4)	11 (9.0)	11 (16.7)	<0.001
Largest nodule class (%)*					<0.001					0.443
<30 mm	1282 (42.1)	46 (35.1)	944 (51.1)	292 (27.3)		86 (35.2)	24 (42.9)	43 (35.2)	19 (28.8)	
30-50 mm	732 (24.0)	30 (22.9)	460 (24.9)	242 (22.6)		44 (18.0)	11 (19.6)	22 (18.0)	11 (16.7)	
>50 mm	1,033 (33.9)	55 (42.0)	443 (24.0)	535 (50.0)		114 (46.7)	21 (37.5)	57 (46.7)	36 (54.5)	
Multiple tumors (vs single) (%)*	502 (17.5)	33 (25.6)	292 (15.6)	177 (20.6)	<0.001	36 (14.8)	11 (19.6)	19 (15.6)	6 (9.1)	0.245
Satellite nodules (presence of) (%)	339 (34.3)	61 (51.3)	250 (34.4)	28 (19.7)	<0.001	49 (20.1)	20 (35.7)	26 (21.3)	3 (4.5)	<0.001
Margins mm (mean (SD))	8.04 (10.22)	7.40 (12.64)	9.06 (10.22)	5.87 (9.37)	<0.001	8.10 (9.39)	5.84 (7.22)	9.23 (9.97)	7.87 (9.67)	0.103
R1 (%)	403 (14.2)	36 (27.5)	175 (9.6)	192 (21.6)	<0.001	37 (15.2)	12 (21.4)	12 (9.8)	13 (19.7)	0.117
Recurrence (%)	1,364 (47.0)	75 (58.6)	821 (45.8)	468 (47.6)	0.017	121 (49.6)	31 (55.4)	58 (47.5)	32 (48.5)	0.839

The * symbol refers to preoperative variables included to calculate the propensity score matching.
AFP, alpha foeto protein; *ASA*, American Society of Anesthesiology; *BMI*, body mass index; *IMM*, Institut Mutualiste Montsouris; M, male; *PVE*, portal vein embolization; *R1*, resection R1; *SD*, standard deviation; *TACE*, transarterial chemoembolization.

Predictors of mortality within the matched cohort

A univariate Cox model was used to determine the influence of liver cancer subtype, liver nodules >5 cm, preoperative AFP level, CA 19-9 level, and R1 status on long-term mortality.

Multivariate analysis adjusted for the previous variables (and including supplementary variables clinically relevant as age, metabolic syndrome, cirrhosis, surgical approach, difficulty of LR as per IMM classification, severe postoperative complications Clavien-Dindo >III, satellite nodules) revealed that liver cancer (reference: HCC; iCCA HR: 6.51, 95% CI (0.13, 320) $P = .3$; cHCC-CCA HR: 6.60, 95% CI (1.20, 36.3) $P = .03$), metabolic syndrome (HR: 45.7, 95% CI (3.22, 651) $P = .005$), preoperative AFP (HR 1.00, 95% CI (1.00, 1.00) $P = .002$) and preoperative CA 19-9 (HR 1.00, 95% CI (0.99, 1.00) $P < .002$) and presence of satellite nodules (HR 71, 95% CI (9.26, 545) $P < .001$) were significantly associated with mortality (Table II).

Disease free survival, before and after matching

Within the whole cohort, Kaplan–Meier DFS estimation at 1, 3, and 5 years were 51%, 29%, and 25% for cHCC-CCA; 71%, 44%, and 31% for HCC group; and 63%, 38%, and 34% for iCCA group, respectively ($P = .0005$) (Supplementary Figure S3).

Figure 4 displays the Kaplan–Meier DFS estimation after matching at 1, 3, and 5 years: 51%, 25%, and 17% for cHCC-CCA; 63%, 35%, and 26% for HCC group; and 51%, 31%, and 28% for iCCA group, respectively ($P = .19$).

Predictors of recurrence within the matched cohort

The univariate Cox model found only the IMM difficulty classification (reference: grade I; grade II HR: 2.24, 95% CI (1.34, 3.77) $P = .002$; grade III HR: 1.38, 95% CI (0.84, 2.25) $P = .2$) as predictor of recurrence within the matched cohort.

Adjusted multivariate analysis (including liver cancer subtype, age, metabolic syndrome, cirrhosis, largest nodule diameter, single versus multiple tumors, preoperative AFP and CA 19-9 serum markers, severe postoperative complications Clavien-Dindo >III, satellite nodules difficulty of LR as per IMM classification, R1 resection and surgical margins) showed that the presence of

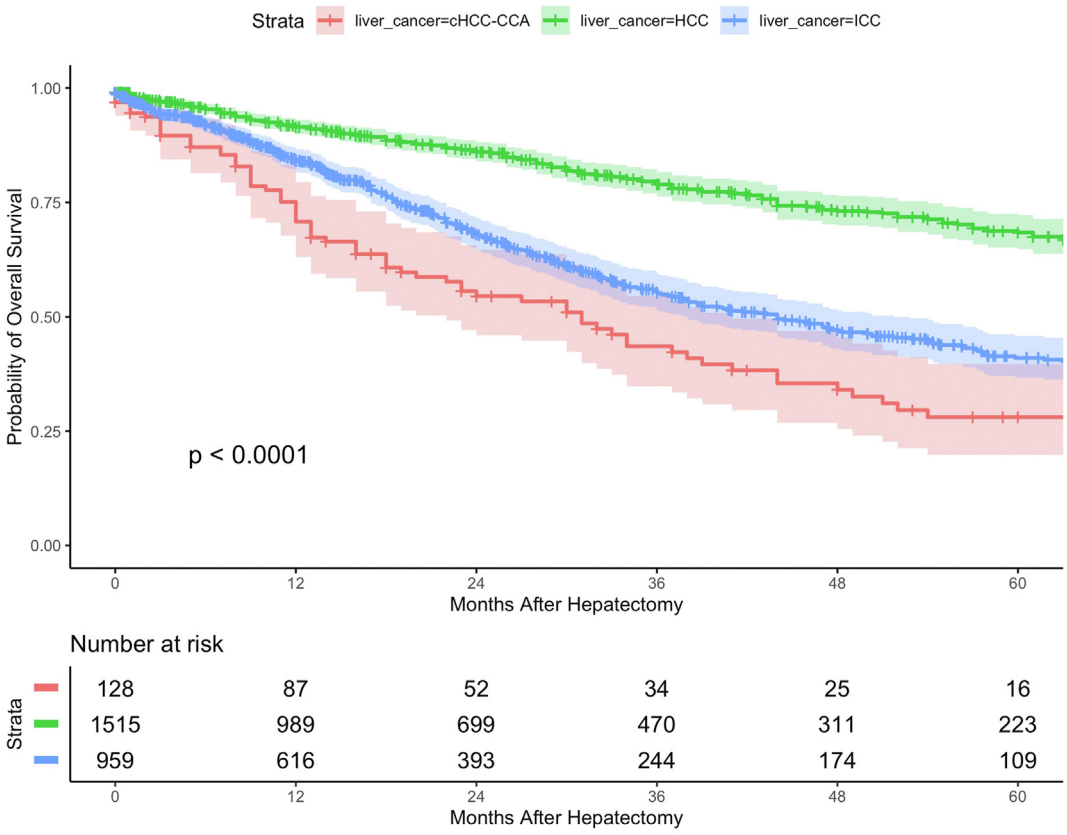

Figure 2. Overall survival (OS) before matching at 1, 3, and 5 years.

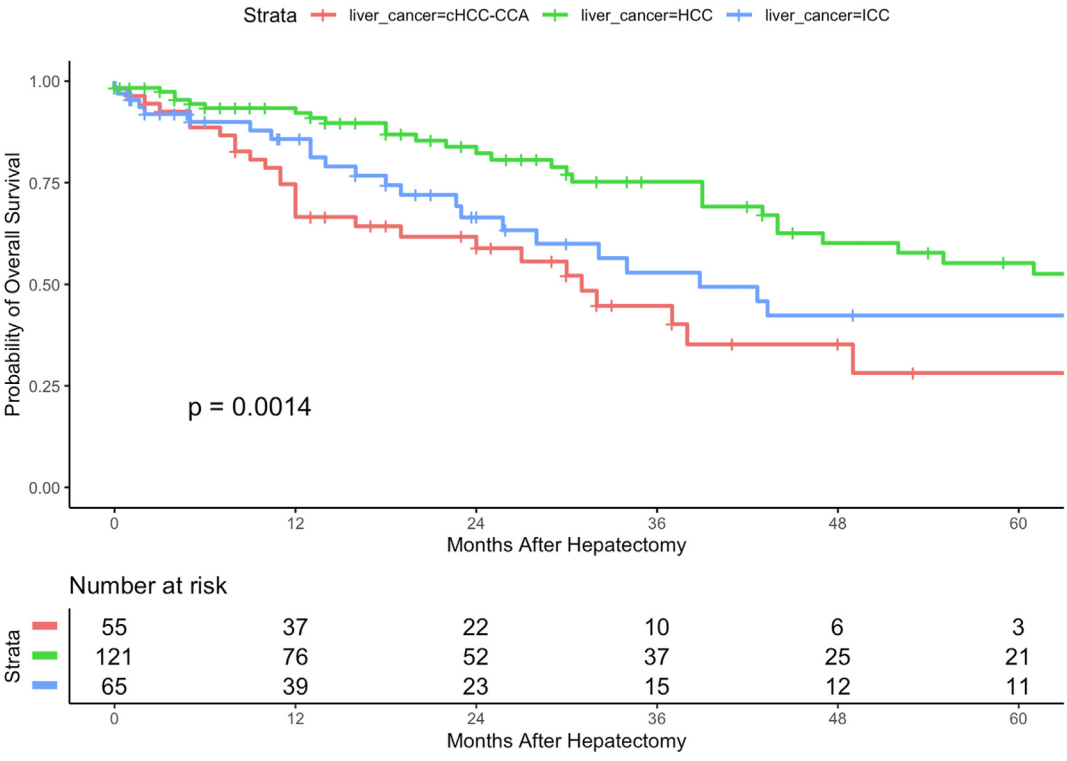

Figure 3. Overall survival (OS) after matching at 1, 3, and 5 years.

Table II
Results of univariable and multivariable Cox analysis predicting death in the matched cohort

	HR	Univariate analysis	*P* value	HR	Multivariate analysis	*P* value
		95% CI			95% CI	
Liver cancer						
HCC	—	—		—	—	
iCCA	1.90	1.13, 3.18	.015	6.51	0.13, 320	.3
cHCC-CCA	2.46	1.46, 4.15	<.001	6.60	1.20, 36.3	.03
Sex						
F	—	—				
M	0.91	0.63, 1.31	.6			
Age, class						
<50 y	—	—		—	—	
50-70 y	0.71	0.33, 1.50	.4	4.42	0.14, 141	.4
>70	0.90	0.41, 1.98	.8	11.2	0.35, 359	.2
Metabolic syndrome						
0	—	—		—	—	
1	1.35	0.95, 1.90	.090	45.7	3.22, 651	.005
ASA						
I	—	—				
II	0.74	0.38, 1.44	.4			
III	0.62	0.32, 1.22	.2			
IV	0.37	0.05, 2.92	.3			
TACE						
0	—	—				
1	1.32	0.54, 3.27	.5			
PVE						
0	—	—		—	—	
1	4.01	1.60, 10.1	.003	1.38	0.50, 3.79	.5
Cirrhosis						
0	—	—		—	—	
1	1.26	0.90, 1.76	.2	1.48	0.09, 25.7	.8
Largest nodule class						
<30 mm	—	—		—	—	
30-50 mm	1.10	0.57, 2.16	.8	0.02	0.00, 1.10	.056
>50 mm	1.83	1.11, 3.01	.017	1.20	0.07, 21.3	>.9
Number of tumors (single vs multiple)						
Single	—	—		—	—	
Multiple	1.07	0.55, 2.07	.8	0.25	0.01, 5.52	0.4
Preoperative AFP						
ng/mL (per unit increase)	1.00	1.00, 1.00	.006	1.00	1.00, 1.00	.002
Preoperative CA 19-9						
U/mL (per unit increase)	1.00	1.00, 1.00	<.001	1.00	0.99, 1.00	<.001
Surgical approach						
Laparoscopic	—	—				
Open	0.73	0.50, 1.06	.10			
IMM						
I	—	—		—	—	
II	1.40	0.69, 2.84	.4	0.26	0.04, 1.60	.15
III	1.43	0.78, 2.60	.2	0.02	0.00, 1.59	.078
Clavien-Dindo ≥III 90d						
0	—	—		—	—	
1	2.03	1.21, 3.40	.008	0.18	0.02, 1.77	.14
Satellite nodules						
0	—	—		—	—	
1	1.29	0.79, 2.12	.3	71.0	9.26, 545	<.001
R1						
0	—	—		—	—	
1	1.74	1.04, 2.90	.034	1.15	0.13, 10.4	>.9
Margins (mm)						
per mm increase	1.02	1.00, 1.04	.13			

AFP, alpha foetoprotein; *ASA*, American Society of Anesthesiology; *BMI*, body mass index; *CI*, confidence interval; *F*, female; *HR*, hazard ratio; *IMM*, Institut Mutualiste Montsouris; *M*, male; *PVE*, portal vein embolization; *TACE*, transarterial chemoembolization.

satellite nodules (HR: 3.2, 95% CI (1.21, 11.1) $P = .036$) were the only predictors of recurrence (Table III).

Discussion

Mixed cHCC-CCA is a rare PLC with a poorly described clinical presentation and grim prognosis. The present study, based on a large, international, hospital-based, and clinician-promoted cohort of patients treated by LR, allowed comparison of cHCC-CCA with both HCC and iCCA. A 2-step matching process with a PS based on 8 preoperative characteristics was used to generate 3 comparable groups with minimal heterogeneity.

Despite the final cohort being smaller than previously published population-based studies,[13–15] the expected loss of patients through the matching process was balanced by the low heterogeneity observed among the 3 groups. The present cohort ($n = 244$) was nevertheless larger than previous series[6] obtained with a pairing process based on 1 or 2 clinical variables.

The long-term overall survival of patients with cHCC-CCA was closer to iCCA rather than HCC patients, as previously reported by

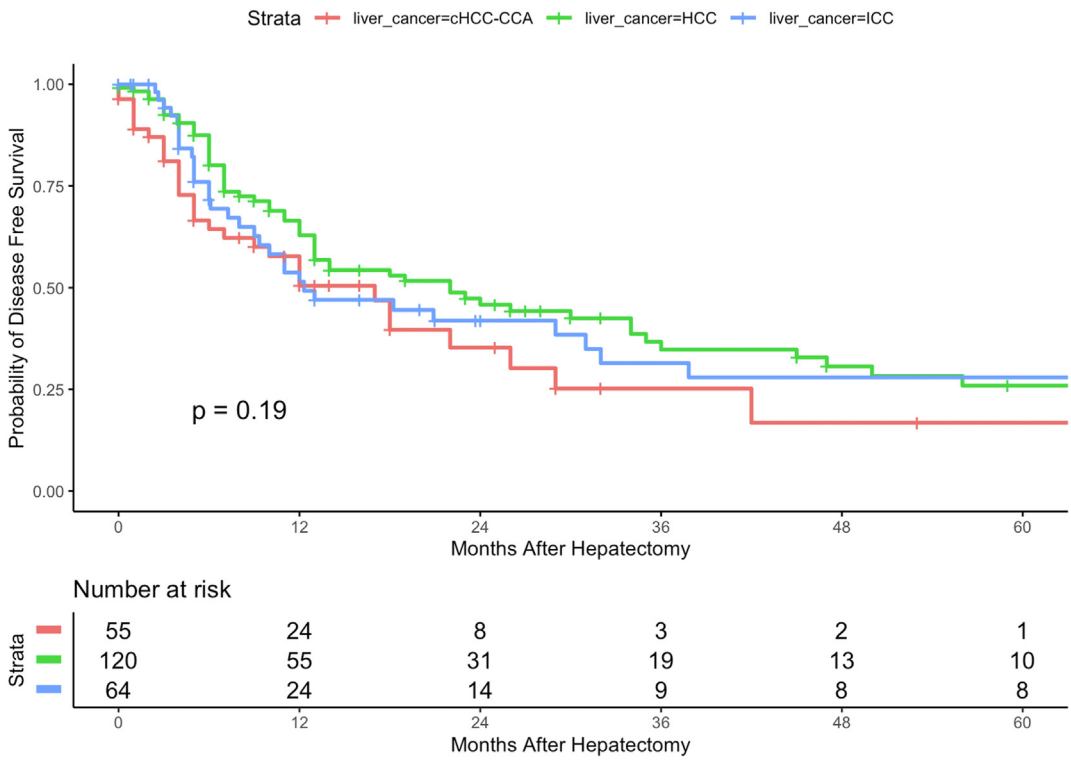

Figure 4. Disease-free survival (DFS) after matching at 1, 3, and 5 years.

Yoon et al[5] on a smaller, unmatched cohort. A recent Western study[6] reported no difference in oncologic outcomes among cHCC-CCA and HCC patients, but it should be noted that both groups were matched only for cirrhosis and tumor size, without any PS matching. The most likely explanation for better overall survival observed among patients affected by HCC (which can still benefit from liver transplantation—despite this variable being seldom available within the databases analyzed) is the relative absence of treatment options when recurrence occurs in cases of cHCC-CCA and iCCA and/or poor response to systemic therapy when offered. Gemcitabine-platinum regimens are currently recommended without the support of strong evidence.[2,16,17]

In the present cohort, predictors of death were cHCC-CCA subtype, metabolic syndrome, preoperative AFP and CA19-9, and the presence of satellite nodules. The negative effect of cHCC-CCA phenotype on survival has been reported,[13] and it might be explained by the combination of heterogeneous genomic features (common to both HCC and iCCA[2]), the immunophenotypic expression of hepatic progenitor cells[18] and their markers (such as Nestin, which is associated with a poor prognosis when expressed[4]), as well as genetic signatures predictive of overexpression of genes related to immune cells recruitment.[3] These variables might become more relevant than traditional clinical characteristics to predict the risk of recurrence or poor response to salvage treatments.[16]

In a large meta-analysis[19] on 15 studies, metabolic syndrome was associated with impaired short-term postoperative outcomes after hepatectomy (overall and severe complications, postoperative hemorrhages, and infection)—hence, with no direct consequences on survival. The relationship between metabolic syndrome, postoperative complications, and impaired survival after LR for both HCC or iCCA might be indirect (similar to a "domino effect"), as suggested by other studies focusing on postoperative complications.[20–23] Another multicenter cohort study[24] on 1,753 patients treated for HCC revealed how the presence of metabolic syndrome predicted the risk of decreased OS, mainly due to early and late recurrence. The authors[24] suggested that the risk of recurrence was probably related to the degrees of liver inflammation, including liver cirrhosis and active hepatitis.

The linear interaction between tumor markers levels (AFP[25–27] and CA19-9[28–30]), increased risk of tumor spread, and impaired survival has been widely reported in the literature, for both HCC and iCCA.

The presence of satellite nodules reflects the aggressiveness of the disease and is extensively reported in the literature as a predictor of death and recurrence, irrespective of histologic subtype (cHCC-CCA,[31,32] HCC,[33,34] or iCCA[35,36]).

When focusing on survival without recurrence, no difference was observed among the 3 histologic groups. These observations are similar to previously published studies on smaller series,[5,6,37] reporting no differences in recurrence after matching for tumor size and stage, number of tumors, cirrhosis, R0 resection, no 90-day mortality, and follow-up.

In the present cohort, recurrence was associated with satellite nodules rather than cancer subtype. As for survival, the presence of satellite nodules reflects the aggressiveness of the disease and is reported in the literature as a predictor of recurrence, (cHCC-CCA,[31,32] HCC,[33,34] or iCCA[35,36]).

This study highlights the importance of repurposing existing clinical databases and cohorts. Although randomized trials generate the highest level of evidence, these are unlikely to be feasible in the field of a rare disease such as cHCC-CCA. Among the alternatives to consider, the reuse of existing clinical databases might be a promising solution in such circumstances, more focused on clinical outcomes than larger administrative databases. We strongly believe in a more responsible, honest, and somehow "sustainable" research: time and money are limited, and the "3R" concept (reduce, reuse, recycle) may also apply in clinical research to reduce the avoidable burden of waste.[38]

Table III
Results of univariable and multivariable Cox analysis predicting recurrence in the matched cohort

	HR	Univariate analysis	*P* value	Multivariate analysis		
		95% CI		HR	95% CI	*P* value
Liver cancer						
HCC	—	—		—	—	
iCCA	1.18	0.77, 1.82	.4	0.36	0.06, 2.17	.3
cHCC-CCA	1.50	0.97, 2.33	.069	1.33	0.38, 4.65	.7
Sex						
F	—	—				
M	1.00	0.66, 1.52	>.9			
Age, class						
<50 y	—	—		—	—	
50-70 y	1.07	0.54, 2.14	.8	0.36	0.02, 7.11	.5
>70	1.13	0.54, 2.36	.7	0.24	0.01, 6.97	.4
Metabolic syndrome						
0	—	—		—	—	
1	1.07	0.72, 1.57	.7	2.63	0.70, 9.96	.2
ASA						
I	—	—				
II	0.75	0.39, 1.47	.4			
III	0.79	0.40, 1.56	.5			
IV	5.85	1.24, 27.6	.026			
Cirrhosis						
0	—	—		—	—	
1	1.19	0.83, 1.72	.3	1.14	0.19, 6.90	.9
Largest nodule class						
<30 mm	—	—		—	—	
30-50 mm	1.06	0.63, 1.77	.8	0.41	0.05, 3.43	.4
>50 mm	1.05	0.70, 1.56	.8	0.41	0.06, 2.63	.3
Number of tumors (single vs multiple)						
Single	—	—		—	—	
Multiple	1.57	0.97, 2.55	.065	4.17	0.66, 26.4	.13
Preoperative AFP						
ng/mL (per unit increase)	1.00	1.00, 1.00	.8	1.00	1.00, 1.00	.5
Preoperative CA 19-9						
U/mL (per unit increase)	1.00	1.00, 1.00	.2	1.00	1.00, 1.00	.6
Surgical approach						
Laparoscopic	—	—				
Open	1.41	0.97, 2.05	.074			
IMM						
I	—	—		—	—	
II	2.24	1.34, 3.77	.002	2.73	0.53, 14.1	.2
III	1.38	0.84, 2.25	.2	2.35	0.10, 53.4	.6
Clavien-Dindo ≥III 90d						
0	—	—		—	—	
1	1.23	0.72, 2.10	.5	4.11	0.69, 24.5	.12
Satellite nodules						
0	—	—		—	—	
1	1.40	0.91, 2.15	.12	3.20	1.21, 11.1	.036
R1						
0	—	—		—	—	
1	1.07	0.66, 1.75	.8	0.31	0.02, 5.07	.4
Margins (mm)						
per mm increase	1.01	0.99, 1.03	.5	1.01	0.87, 1.17	>.9

AFP, alpha foeto protein; ASA, American Society of Anesthesiology; BMI, body mass index; CI, confidence interval; F, female; HR, hazard ratio; IMM, Institut Mutualiste Montsouris; M, male; PVE, portal vein embolization; TACE, transarterial chemoembolization.

All classical limits affecting multicenter retrospective series apply to the present study: different case-mix and hospital caseload, evolving knowledge in preoperative diagnosis and surgical expertise over such a long accrual period (even if no survival differences were observed between the 2 decades), the single modality of care (surgery), as well as evolving expertise in pathological diagnosis (historical bias), without mentioning missing key variables (adjuvant chemotherapy, blood loss, postoperative complications, N status, number of nodes, modality of recurrence and treatment). The absence of variables such as lymphadenectomy weighs particularly heavily among the limitations of this study: with 15% of missing observations, this variable could not be analyzed without introducing supplementary biases. With this limit in mind, we can simply report (and without any inference) that the rates of patients undergoing lymphadenectomy within the matched cohort were: overall 19.7%, cHCC-CCA 17.9%, HCC 4.1%, and iCCA 50.0%. Evidence suggests that patients with cHCC-CCA suffer a natural history similar to those affected by iCCA, and given the similar lymphatic pattern of tumor spread, it follows that a routine hilar lymphadenectomy is indicated.[2] Despite this knowledge, the performance of adequate lymphadenectomy is still poorly adhered to, as suggested by the low rate observed here (without considering missing observations), while the postoperative nature of the diagnosis is a likely contributing factor. The precise role of lymphadenectomy at this point remains unresolved.

Another methodologic limitation to be pointed out is the 2-step sequential matching, developed to compensate for the lack of a dedicated statistical library with which to perform a PS matching

on 3 groups. The consequence was the drastic loss of patients through the process, thus limiting the effect of the initially large cohort.

In conclusion, despite data limitations, overall survival observed among patients with cHCC-CCA was closer to iCCA and worse than HCC patients, whereas recurrence rates were similar to both HCC and iCCA controls. Survival and recurrence were influenced by the aggressiveness of the disease, expressed through proxy variables such as cHCC-CCA subtype and satellite nodules.

Research focusing on the biological and molecular profile of cHCC-CCA may lead to improved prediction of prognosis and long-term outcome of this unique oncologic population,[5] define the need for routine lymphadenectomy,[2] and facilitate selection of targeted systemic therapies.[13]

Funding/Support

None declared.

Conflict of interest/Disclosure

None declared.

References

1. Calderaro J, Ziol M, Paradis V, Zucman-Rossi J. Molecular and histological correlations in liver cancer. *J Hepatol*. 2019;71:616–630.
2. Gigante E, Paradis V, Ronot M, et al. New insights into the pathophysiology and clinical care of rare primary liver cancers. *JHEP Reports Innov Hepatol*. 2020;3.
3. Nguyen CT, Caruso S, Maille P, et al. Immune profiling of combined hepatocellular- cholangiocarcinoma reveals distinct subtypes and activation of gene signatures predictive of response to immunotherapy. *Clin Cancer Res*. 2022;28:540–551.
4. Calderaro J, Di Tommaso L, Maillé P, et al. Nestin as a diagnostic and prognostic marker for combined hepatocellular-cholangiocarcinoma. *J Hepatol*. 2022;77:1586–1597.
5. Yoon YI, Hwang S, Lee YJ, et al. Postresection outcomes of combined hepatocellular carcinoma-cholangiocarcinoma, hepatocellular carcinoma and intrahepatic cholangiocarcinoma. *J Gastrointest Surg*. 2016;20:411–420.
6. Holzner ML, Tabrizian P, Parvin-Nejad FP, et al. Resection of mixed hepatocellular-cholangiocarcinoma, hepatocellular carcinoma, and intrahepatic cholangiocarcinoma. *Liver Transpl*. 2020;26:888–898.
7. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet*. 2007;370:1453–1457.
8. Farges O, Fuks D, Le Treut YP, et al. AJCC seventh edition of TNM staging accurately discriminates outcomes of patients with resectable intrahepatic cholangiocarcinoma. *Cancer*. 2011;117:2170–2177.
9. Brustia R, Langella S, Kawai T, et al. Preoperative risk score for prediction of long-term outcomes after hepatectomy for intrahepatic cholangiocarcinoma: report of a collaborative, international-based, external validation study. *Eur J Surg Oncol*. November 2019. https://doi.org/10.1016/j.ejso.2019.10.041
10. Kawaguchi Y, Fuks D, Kokudo N, Gayet B. Difficulty of laparoscopic liver resection. *Ann Surg*. 2018;267:13–17.
11. Kawaguchi Y, Hasegawa K, Tzeng C-WD, et al. Performance of a modified three-level classification in stratifying open liver resection procedures in terms of complexity and postoperative morbidity. *Br J Surg*. October 2019. https://doi.org/10.1002/bjs.11351
12. Dindo D, Demartines N, Clavien P-A. Classification of surgical complications. *Ann Surg*. 2004;240:205–213.
13. Spolverato G, Bagante F, Tsilimigras D, Ejaz A, Cloyd J, Pawlik TM. Management and outcomes among patients with mixed hepatocholangiocellular carcinoma: A population-based analysis. *J Surg Oncol*. 2019;119:278–287.
14. Wang J, Li Z, Liao Y, et al. Prediction of survival and analysis of prognostic factors for patients with combined hepatocellular carcinoma and cholangiocarcinoma: a population-based study. *Front Oncol*. 2021;11. https://doi.org/10.3389/FONC.2021.686972.
15. Ramai D, Ofosu A, Lai JK, Reddy M, Adler DG. Combined hepatocellular cholangiocarcinoma: a population-based retrospective study. *Am J Gastroenterol*. 2019;114:1496–1501.
16. Trikalinos NA, Zhou A, Majella Doyle MB, et al. Systemic therapy for combined hepatocellular-cholangiocarcinoma: a single-institution experience. *JNCCN J Natl Compr Cancer Netw*. 2018;16:1193–1199.
17. Salimon M, Prieux-Klotz C, Tougeron D, et al. Gemcitabine plus platinum-based chemotherapy for first-line treatment of hepatocholangiocarcinoma: an AGEO French multicentre retrospective study. *Br J Cancer*. 2018;118:325–330.
18. Kim M, Hwang S, Ahn CS, et al. Postresection prognosis of combined hepatocellular carcinoma-cholangiocarcinoma cannot be predicted by the 2019 World Health Organization classification. *Asian J Surg*. 2021;44:1389–1395.
19. Murtha-Lemekhova A, Fuchs J, Feiler S, et al. Is metabolic syndrome a risk factor in hepatectomy? A meta-analysis with subgroup analysis for histologically confirmed hepatic manifestations. *BMC Med*. 2022:20.
20. Amini N, Margonis GA, Kim Y, Wilson A, Gani F, Pawlik TM. Complication timing impacts 30-d mortality after hepatectomy. *J Surg Res*. 2016;203:495–506.
21. Margonis GA, Sasaki K, Andreatos N, et al. Prognostic impact of complications after resection of early stage hepatocellular carcinoma. *J Surg Oncol*. 2017;115:791–804.
22. Brustia R, Fleres F, Tamby E, et al. Postoperative collections after liver surgery: Risk factors and impact on long-term outcomes. J Visc Surg. September 2019. https://doi.org/10.1016/j.jviscsurg.2019.09.005
23. van Keulen AM, Büttner S, Erdmann JI, et al. Major complications and mortality after resection of intrahepatic cholangiocarcinoma: a systematic review and meta-analysis. *Surgery*. 2022. https://doi.org/10.1016/J.SURG.2022.11.027.
24. Wang M Da, Tang SC, Li C, et al. Association of concurrent metabolic syndrome with long-term oncological prognosis following liver resection for hepatocellular carcinoma among patients with chronic hepatitis B virus infection: a multicenter study of 1753 patients. *Ann Surg Oncol*. 2023;30:346–358.
25. Nguyen-Khac V, Brustia R, Rhaiem R, et al. Liver resection for single large hepatocellular carcinoma: a prognostic factors study. *Ann Hepatol*. 2022;27.
26. Sessa A, Mulé S, Brustia R, et al. Macrotrabecular-massive hepatocellular carcinoma: light and shadow in current knowledge. *J Hepatocell Carcinoma*. 2022;9:661–670.
27. Assalino M, Terraz S, Grat M, et al. Liver transplantation for hepatocellular carcinoma after successful treatment of macrovascular invasion. *Transpl Int*. January 2020:tri.13586.
28. Izquierdo-Sanchez L, Lamarca A, La Casta A, et al. Cholangiocarcinoma landscape in Europe: diagnostic, prognostic and therapeutic insights from the ENSCCA Registry. *J Hepatol*. 2022;76:1109–1121.
29. Moazzam Z, Alaimo L, Endo Y, et al. Combined tumor burden score and carbohydrate antigen 19-9 grading system to predict outcomes among patients with intrahepatic cholangiocarcinoma. *J Am Coll Surg*. 2023;236:804–813.
30. Zhang G, Chen B-W, Yang X-B, et al. Prognostic analysis of patients with combined hepatocellular-cholangiocarcinoma after radical resection: a retrospective multicenter cohort study. *World J Gastroenterol*. 2022;28:5968–5981.
31. Ma KW, Ho Chok KS. Importance of surgical margin in the outcomes of hepatocholangiocarcinoma. *World J Hepatol*. 2017;9:635–641.
32. Gentile D, Donadon M, Lleo A, et al. Surgical treatment of hepatocholangiocarcinoma: a systematic review. *Liver Cancer*. 2020;9:15–27.
33. Zeng J, Zeng J, Lin K, et al. Development of a machine learning model to predict early recurrence for hepatocellular carcinoma after curative resection. *Hepatobiliary Surg Nutr*. 2022;11:176–187.
34. Famularo S, Piardi T, Molfino S, et al. Factors affecting local and intra hepatic distant recurrence after surgery for HCC: an alternative perspective on microvascular invasion and satellitosis. A Western European multicentre study. *J Gastrointest Surg*. January 2020. https://doi.org/10.1007/s11605-019-04503-7
35. Bagante F, Spolverato G, Cucchetti A, et al. Defining when to offer operative treatment for intrahepatic cholangiocarcinoma: a regret-based decision curves analysis. *Surgery*. 2016;160:106–117.
36. Kang SH, Choi YR, Lee W, et al. Laparoscopic liver resection versus open liver resection for intrahepatic cholangiocarcinoma: 3-year outcomes of a cohort study with propensity score matching. *Surg Oncol*. 2020;33:63–69.
37. Gentile D, Donadon M, Di Tommaso L, et al. Is the outcome after hepatectomy for transitional hepatocholangiocarcinoma different from that of hepatocellular carcinoma and mass-forming cholangiocarcinoma? A case-matched analysis. *Updates Surg*. 2020;72:671–679.
38. Chalmers I, Glasziou P. Avoidable waste in the production and reporting of research evidence. *Lancet*. 2009;374:86–89.