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Clinical Characterization of HCC/CCA Mixed Cancers in a Population-based Cohort

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ABSTRACT

Background & Aims: Primary liver cancer (PLC) ranks among of the most common cancers worldwide. Within this group, a minority of cases displays characteristics of both hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (iCCA), known as combined hepatocellular cholangiocarcinoma (cHCC-CCA). Currently, there is no specific standardized therapy for these mixed tumors. Therefore, the aim of our study was to analyze the clinical course, treatment and outcome of cHCC-CCA patients in a European population-based registry.

Methods: We investigated 9,144 patients with PLC (6,622 HCC, 2,356 iCCA, and 166 cHCC-CCA) diagnosed between 2009 and 2020. All data were obtained from Clinical Cancer Registry of Baden-Württemberg (BW), Germany.

Results: In all three groups patients were predominantly male (82%, 57%, and 68% for HCC, iCCA and cHCC-CCA groups, respectively). 48% of cHCC-CCA patients were diagnosed as stage IV cancers, which was more than for HCC (31%) but less compared to CCA (64%). Overall median survival of cHCC-CCA patients was worse compared to HCC (9-13 months vs. 15.5 months, $p<0.001$) and rather comparable to CCA (11.8 months).

Conclusions: Our data demonstrated that cHCC-CCA tumors appear to have a distinct clinical course with worse overall survival compared to HCC. Thus, identification of these cancers by histopathology is essential in order to further characterize this tumor entity and to provide accurate treatment to these patients.

Key words: combined hepatocellular cholangiocarcinoma – intrahepatic cholangiocarcinoma – hepatocellular carcinoma – histological diagnosis – survival.

Abbreviations: CCA: cholangiocarcinoma; cHCC-CCA: combined hepatocellular cholangiocarcinoma; HCC: hepatocellular carcinoma; iCCA: intrahepatic CCA; LI-RADS: Liver Imaging Reporting and Data System; LR: liver resection; LT: liver transplantation; MRI: magnetic resonance imaging; OS: overall survival; PFS: progression-free survival; PLC: primary liver carcinoma; RFA: radiofrequency ablation; TACE: transarterial chemoembolization.

INTRODUCTION

Combined hepatocellular cholangiocarcinoma (cHCC-CCA) is a biphenotypic tumor with both hepatocytic and cholangiocytic differentiation. Allen and Lisa first described the tumor as cHCC-CCA in 1949 [1]. Compared to hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (iCCA), cHCC-CCA is much rarer, with an estimated incidence of 1% to 4.7% among primary liver carcinomas (PLCs), according to the last WHO Classification [2]. Like other liver cancers, cHCC-CCA is predominantly observed in male patients and the average age at diagnosis is 60-65 years [3-5].

In contrast to HCC and CCA, the management of cHCC-CCA is not yet standardized, and various therapeutic options have been proposed. Resection with lymph node dissection is the only curative option for patients with cHCC-CCA. However, tumor recurrence is frequent (up to 80% at 5 years) and 5-year survival rates do not exceed 30% [4-7]. In general, the prognosis of cHCC-CCA is worse than that of HCC but better or equal to that of iCCA [4-7]. Liver resection (LR) improves the 1- and 5-year overall survival (OS) to 63.9% and 39.5%, respectively, and the median survival to 20.5 months [7]. Liver transplantation (LT) could offer better outcomes

than LR but is indicated and well defined only in HCC patients with limited disease, as defined e.g. by the Milan [8] or UCSF criteria [9]. However, LT is contraindicated in iCCA and its role in cHCC-CCA has not been established yet [10].

Systemic therapy for unresectable PLCs is evolving but very diverse for HCC and iCCA. Atezolizumab/bevacizumab is now the first-line therapy for patients with advanced HCC [11, 12], after the IMbrave150 demonstrated superiority against sorafenib, with comparable safety profiles [13]. Moreover, the HIMALAYA trial evaluated tremelimumab (CTLA-4 inhibitor) plus durvalumab (PD-1 inhibitor) showing superiority against sorafenib in HCC patients and obtained approval [14]. Regarding iCCA, therapy had remained unchanged since the ABC 02 trial established cisplatin/gemcitabine as the treatment of choice in 2010 [15]. The interim analysis of the phase III TOPAZ-1 trial, evaluated durvalumab as an add-on to the current therapy, and proved to be superior to cisplatin/gemcitabine alone [16]. Unfortunately, the evidence available is limited for cHCC-CCA but seems to favor the combination of cisplatin/gemcitabine over sorafenib [17, 18], with most studies including small sample sizes and a retrospective approach [19-21].

Given these differences in therapy options and outcomes upon proper treatment, a correct diagnosis is essential to the patient´s survival. A histopathological approach might provide a better insight into the tumor's biology, which can be translated into an improvement in PLC patients' management. Nevertheless, regarding cHCC-CCA, much more investigation is required. In this study we described the clinical characteristics, treatment, and outcome of a population-based cohort of cHCC-CCA patients diagnosed between 2009 and 2020 and reported to the Clinical Cancer Registry of Baden-Württemberg in Germany.

METHODS

Patients were selected from the Clinical Cancer Registry database (Klinisches Landeskrebsregister, KLR) of the German Federal State Baden-Württemberg (BW) with a population of over 11 million in 2019. The KLR BW collects standardized clinical, diagnostic, treatment, and follow-up information for all patients that are diagnosed with cancer in the BW State.

Overall, 9,134 adult patients (> 17 years) diagnosed between 2009 and 2020 were selected by ICD-10 (C22) and by histology defined as HCC (8170, 8171, 8172, 8173, 8174); CCA (8160, 8503, 8161, 8470), and cHCC-CCA (8180) according to the International Classification of Diseases for Oncology, Third Edition (ICD-O-3). The steps of the selection procedure are illustrated in Fig. 1.

Different types of first-line treatments were categorized as follows: surgical resection, locoregional treatment [transarterial chemoembolization (TACE), radiotherapy], and systemic therapy. Surgical approach including transplantation and radiofrequency ablation (RFA) are considered curative treatment options for this disease. Since there is not any generally accepted standard first line therapy for advanced cHCC-CCA, clinicians may choose either a therapy standardly applied for HCC or for CCA patients in advanced stage. Non-surgical treatment options include TACE and systemic therapy. In contrast to surgery, the role of systemic therapy in cHCC-CCA remains unclear.

Patients that were not residents of BW were excluded from the survival analysis as their follow-up data may be incomplete.

Statistical Analysis

Descriptive statistics of patient and tumor characteristics (age, gender, TNM stage, lymph node involvment) was provided for all selected patients. The Kaplan-Meier method was employed to obtain survival rates for each histology or treatment group and the log-rank p-test was utilized to assess whether the difference between groups was statistically significant. Overall survival as well as the progression-free survival (PFS) were analyzed. The latter was defined as the time interval from the diagnosis until the reported progression or death, whatever came first; patients without progression at the last follow-up were censored at the time of last reported information. Important parameters (such as gender, stage, and histology diagnosis group) were further examined by a multivariate Cox proportional hazards regression analysis.

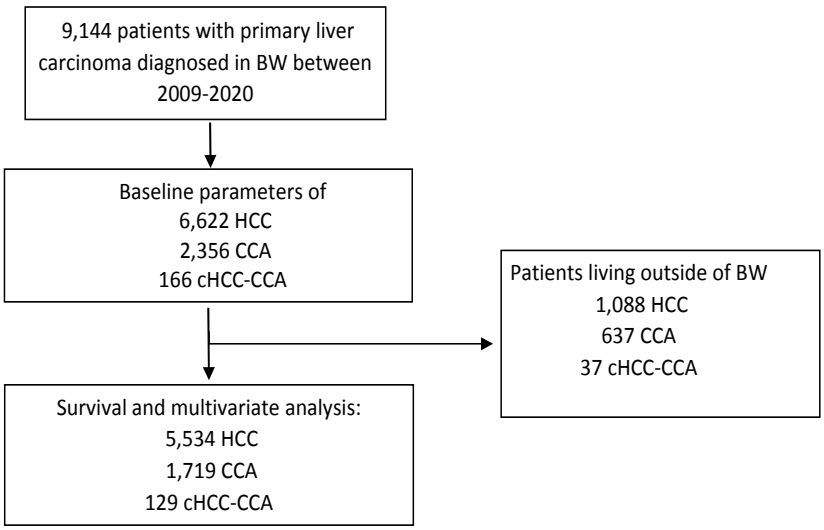

Fig. 1. Flowchart showing the selection of the patients.

RESULTS

Patient Demographics and Clinical Information

Among 9,144 patients included in the analysis, 6,622, 2,356, and 166 were identified as HCC, iCCA and cHCC-CCA groups, respectively. Table I illustrates patient demographics and clinical information. For cHCC-CCA and iCCA, diagnosis was obtained from the pathology report, whereas for HCC, about 22% of cases were clinically diagnosed. 62% of cHCC-CCA patients were older than 65 years, which was comparable to HCC (64%) but more than for CCA (55%). In all three groups patients were predominantly males (Table I). 52% of cHCC-CCA patients were diagnosed as stage IV cancers, which was more than for HCC (33%) but less compared to CCA (65%). The fraction of patients with regional lymph node infiltration (N+) was 13% in the HCC group and 46% and 33% for iCCA and cHCC-CCA groups. Lymph vessel infiltration (L1) was reported more frequently for the iCCA group (30%) and less for the cHCC-CCA (19%) and HCC (9%) groups. Common sites of distant metastasis in HCC were lung (38%) and bones (31%). The metastatic localization in cHCC-CCA patients was more similar to iCCA as compared to HCC. They preferentially metastasized to the liver (34% for cHCC-CCA and 54% for iCCA) and distant lymph nodes (48% and 30% respectively) Table II describes the stages for the BW resident patients used for survival curves.

Oncological Outcome According to Histology

The results of the Kaplan-Meier survival analysis were shown in Fig. 2A. The two-year overall survival of the patients in the cHCC-CCA group were found to be notably worse compared to the HCC group (9-13 months vs. 15.5 months, $p<0.001$) but comparable with the CCA group (11.8 months). The multivariate analysis showed that tumor stage was an important prognosis factor (Fig. 3A). Interestingly, the multivariate Cox regression analysis demonstrated that HCC histology group had a worse prognosis compared to iCCA and cHCC-CCA (HR=1.21, 95%CI: 1.09-1.3). However, most patients with cHCC-CCA and CCA were diagnosed at an advanced stage, which may explain the better clinical outcome for this group observed in the univariate OS analysis.

Results of the PFS analysis shown in Fig. 2B demonstrated that the iCCA group had a better outcome compared to cHCC-CCA (with 7.2, 8.8 and 11 months of progress-free time for cHCC-CCA, iCCA and HCC, respectively). Here again, the multivariate analysis suggested that tumor stage was an important prognosis factor (Fig. 3B).

Treatment Modalities in cHCC-CCA Patients

We analyzed 79 patients with cHCC-CAA and available information about first line treatment (Table III). 31 patients underwent liver resection; 7 of those received adjuvant therapy. 6 patients underwent re-resection within 3-6 months after

Table I. Baseline clinical and patient characteristics

	Overall, n, 9,144	HCC, n (%) 6,622 (72.4)	CCA, n (%) 2,356 (25.8)	cHCC-CCA, n (%) 166 (1.8)
Gender, n (%)				
Male	6861 (75)	5406 (82)	1344 (57)	111 (68)
Female	2235 (25)	1178 (18)	1004 (43)	53 (32)
Unspecified	48	38	8	2
Age, years				
median (SD)	69 (11.1)	70 (10.7)	67 (11.9)	69.5 (12.1)
> 65	5,636	4,236 (64%)	1,297 (55%)	103 (62%)
range	18-95	18-95	22-94	24-93
TNM Stage, n (%)				
I	949	752 (26)	176 (12)	21 (25)
II	841	658 (22)	173 (12)	10 (12)
III	740	565 (19)	166 (11)	9 (11)
IV	1970	954 (33)	973 (65)	43 (52)
No data	4,644	3,693	868	83
N category, n (%)				
N0	3,148 (77)	2,481 (87)	617 (54)	50 (33)
N+	922 (23)	366 (13)	531 (46)	25 (67)
No data	5,074	3,775	1,208	91
Metastases, n (%)	1,622 (17.7)	762 (11.5)	825 (35)	35 (21)
Liver	572 (35)	111 (15)	449 (54)	12 (34)
Lymph nodes	435 (27)	167 (22)	251 (30)	17 (48)
Bones	372 (23)	239 (31)	127 (15)	6 (17)
Lung	505 (31)	291 (38)	205 (25)	9 (26)

CCA: cholangiocarcinoma; cHCC-CCA: combined hepatocellular cholangiocarcinoma; HCC: hepatocellular carcinoma.

initial surgery. Two patients received RFA. 13 patients were treated with TACE. Among 20 patients who received systemic therapy, 14 underwent chemotherapy, six targeted therapy and one immunotherapy (Table III).

Table II. Frequencies of the different stages at diagnosis of patients living within the area of BW

Stage, n (%)	I	II	III	IV
HCC	666 (26.3)	583 (23)	490 (19.4)	793 (31.33)
CCA	138 (12.7)	127 (11.8)	129 (11.9)	689 (63.6)
cHCC-CCA	16 (25)	9 (14)	8 (12.5)	31 (48.4)

For abbreviations see Table I.

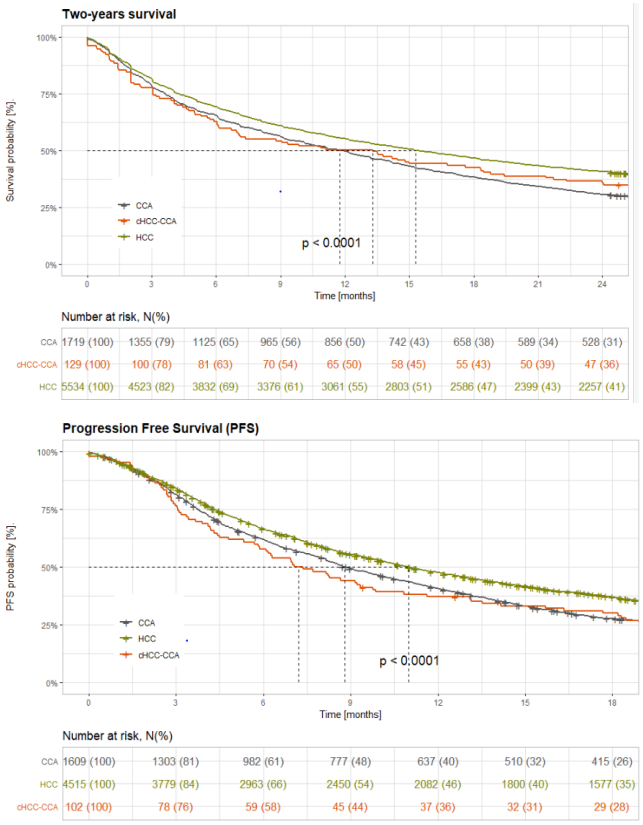

Fig. 2. Survival analysis. A) Overall-survival in cHCC-CCA patients versus HCC and CCA patients after 2 years. Pairwise log-rank test, p<0.0001; B) Progression free survival in cHCC-CCA patients versus HCC and CCA.

Outcome of Patients with cHCC-CCA Treated without Surgery

Results of the OS analysis for cHCC-CCA patients treated with chemotherapy and TACE are illustrated in Fig. 4. The survival outcome for these patients was clearly worse for the patients who underwent chemotherapy relative to those treated with TACE (overall median survival 17-month, p=0.02). However, both patient groups were rather small.

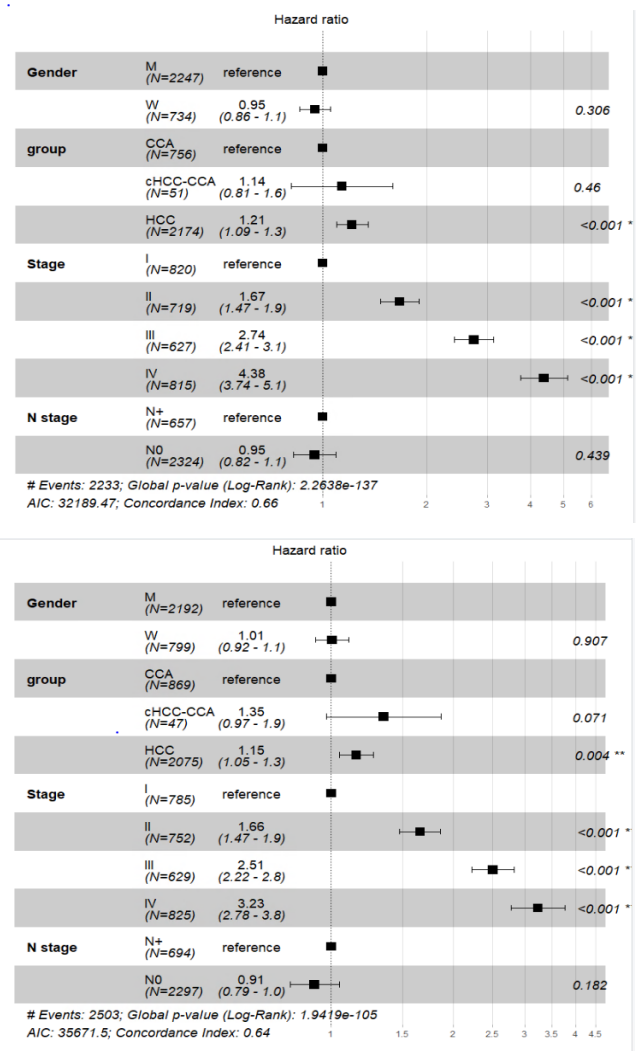

Fig. 3. Multivariate Cox regression analysis of the risk factors. The analysis is performed for patients with complete set of data only: A) For overall survival; B) For progression-free survival

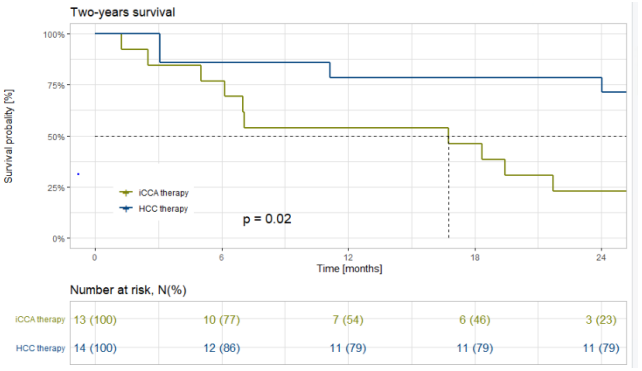

Fig. 4. Overall survival curves of patients with cHCC-CCA according to non-operative treatment. CCA-line: CCA-like therapy, HCC-line: HCC-like therapy.

DISCUSSION

Investigating cHCC-CCA, its diagnosis and clinical course, the dilemma starts with the diagnosis of this subtype and estimation of its frequency. Due to a lack of consequent histopathological diagnosis, and HCC diagnosis rather than being established by means of radiological criteria (which is covered by current clinical practice guidelines) [11-12], the true frequency of this tumor must be assumed to be underestimated since imaging may not be able to distinguish between HCC

Table III. An overview of the treatment modalities for 79 patients with cHCC-CCA

Reported primary treatment modalities	N = 79	Treatment recommended for
Hepatic resection only	24	
Hepatic resection with adjuvant chemotherapy	6	
Hepatic resection with adjuvant radiation	1	
Local ablation		
TACE	13	HCC
SIRT	3	
RFA/ microwave	2	
Chemotherapy		
Cisplatin/Gemcitabin	6	CCA
Gemcitabin	5	CCA
FOLFIRI	1	CCA
Doxorubicin*	1	HCC
Oxaliplatin*	1	CCA
Targeted therapy		
Sorafenib	4	HCC
Lenvatinib	1	HCC
Immunotherapy		
Atezolizumab/Bevacizumab	1	HCC

According to NCCN Guideline combination therapy rather than single agents recommended (Doxorubicin+Cisplatin; Oxaliplatin+ 5-FU, Capecitabine or Gemcitabine). CCA: cholangiocarcinoma; cHCC-CCA: combined hepatocellular cholangiocarcinoma; HCC: hepatocellular carcinoma; RFA: radiofrequency ablation; TACE: transarterial chemoembolization.

and cHCC-CCA. In our comparative analysis of patients, the prevalence of cHCC-CCA was found to be 1.8% (166 patients) among all patients with PLC. This is in line with a recently reported Asian cohort [6].

Like other liver malignancies, cHCC-CCA was predominantly observed in male patients. The mean age in our study was slightly higher as previously reported from the SEER database (70 vs. 62 years) [3-5]. For all three PLCs most tumors were diagnosed in stage IV. This was in accordance with the results from the U.S.A. [4]. However, for HCC we observed a tendency to be detected at earlier stages compared to CCC, but also cHCC-CCA. As it has been discussed before that cHCC-CCA also have the best prognosis when undergoing surgery [4], the need of effective surveillance of patients and risk and early detection strategies must again be emphasized.

In our large European cohort on PLC, cHCC-CCA also has a worse survival than HCC but is better or comparable to iCCA, which is in line with U.S. and Asian cohorts [6, 7]. It is important to note that different treatment modalities for patients with cHCC-CCA were rather evenly distributed between therapies commonly employed for HCC and iCCA (Table III). Tang et al. [7] observed that lymph node infiltration and postoperative TACE were independent prognosis factors after comparing cHCC-CCA patients with HCC and iCCA with similar risk factors. They also found that cirrhosis frequency was comparable between cHCC-CCA and HCC. Nevertheless, these baseline characteristics were not associated with different survival [7]. Yen et al. [6] found that stage IV was associated with a worse prognosis in OS [6]. Our multivariate analysis further supported this observation that tumor stage was an important prognosis factor, again showing the need of effective surveillance of patients at risk (cirrhosis, high grade fibrosis, hepatitis B, chronic cholestatic liver disease).

Noteworthy, Yen et al. [6] pointed out on their Asian cohort that HCC with stem cell features (HCCscf) had a better survival than cHCC-CCA. This is relevant since HCC with stem cell features was previously considered a subtype of cHCC-CCA but after the updated WHO classification system in 2019, it was reallocated to HCC. This highlights the importance of a proper diagnosis since it has prognostic implications. For histopathological diagnosis no more than routine hematoxylin-eosin staining is required, with both components adjoining each other, deeply intermingled or even merged [22]. Radiologic findings of cHCC-CCA on gadoxetic acid-enhanced magnetic resonance imaging may include features of either or both phenotypes: arterial hyperenhancement, washout appearance and enhancing capsule for the HCC component [23], and rim enhancement in the arterial phase as well as targetoid appearance in the hepatobiliary phase for the iCCA counterpart [24].

The current diagnostic algorithm favors, however, the radiological approach since 75-85% of all PLCs will be HCC [25]. In this regard, the Liver Imaging Reporting and Data System (LI-RADS), created to assist the radiological diagnosis of PLC, particularly HCC [28], included the categories LI-RADS 4 and 5 (probably and definitely HCC) and LI-RADS-M (probably or definitely malignant but not HCC specific), which were important in the differential diagnosis of HCC.

The performance of LI-RADS to differentiate cHCC-CCA from HCC has been evaluated in different settings. In a cohort of 152 patients with cHCC-CCA treated with surgery, 48.7% of patients with risk factors for HCC (cirrhosis or HBV infection) were classified as LI-RADS 4 or 5, while 63.6% of those without risk factors were classified as LI-RADS M. LI-RADS 4/5 categories were associated with better survival in multivariate analysis. In total, 50% of cHCC-CCA cases were misclassified as HCC [29]. In another study, HCC cases were matched with iCCA and cHCC-CCA cases according to the magnetic resonance imaging (MRI) strength field (1.5 or 3 T). The sensitivity of the LI-RADS M or LI-RADS-TIV (tumor in vein) category for diagnosing cHCC-CCA was 41.67%. Of 24 cHCC-CCA cases, 45.83% were classified as LI-RADS 5. Although the specificity was high, sensitivity was suboptimal in differentiating HCC from non-HCC [30]. A different approach employing radiomics and machine learning to differentiate between the three tumors, found an AUC of 0.77 to differentiate cHCC-CCA from HCC and iCCA using the late venous phase of MRI, and an AUC of 0.79-0.81 when all phases of contrasted-MRI were included, to distinguish between HCC and non-HCC but, its implementation into the clinical practice is to be further investigated [31]. This demonstrates that performance of LI-RADS v2018 in diagnosing cHCC-CCA is still challenging. A two-step approach in the diagnosis of cHCC-CCA, i.e., radiological assessment and histopathological analysis, has shown to improve diagnosis efficiency [32].

Histopathological diagnosis of HCC, particularly in cirrhotic patients, has been historically discouraged [27] mostly pointing out a theoretical 2.7% risk of tumor seeding after needle biopsy [33] and a risk of severe bleeding in less than 0.5% cases [34]. Nevertheless, as new evidence emerges, liver biopsy seems to have an important role in diagnosis accuracy, identification of therapeutic targets, and prognosis [35]. The current German guidelines have precise indications for the performance of biopsies, favoring their implementation before the inclusion of patients in clinical trials, treatments with curative intent, or patients managed in a palliative manner, due to the therapeutic implications involved [36]. As more biopsies in the context of PLCs are obtained, the true incidence of cHCC-CCA can be estimated with greater certainty, as well as the inclusion of such patients in clinical trials, which, as in HCC, may improve their prognosis.

CONCLUSIONS

Our large retrospective population-based study demonstrated that cHCC-CCA tumors appear to have a distinct clinical course with worse overall survival compared to HCC. Our data support more frequent histological diagnosis to exclude or confirm cHCC-CCA as a basis for a more adequate therapy assignment.

Conflicts of interest: None to declare.

Authors' contribution: P.M. and I.S. conceived and designed the study. I.S., C.W. and G.S. collected the data. D.K. and I.S. performed statistical analyses. A.T. and I.R. wrote the initial manuscript. M.E. supervised the project. All authors worked on the manuscript and agree with the manuscript's results and conclusions.

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