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Review

Combined Hepatocellular-Cholangiocarcinoma: What the Multidisciplinary Team Should Know

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Abstract: Combined hepatocellular-cholangiocarcinoma (cHCC-CCA) is a rare type of primary liver malignancy. Among the risk factors, hepatitis B and hepatitis C virus infections, cirrhosis, and male gender are widely reported. The clinical appearance of cHCC-CCA is similar to that of HCC and iCCA and it is usually silent until advanced states, causing a delay of diagnosis. Diagnosis is mainly based on histology from biopsies or surgical specimens. Correct pre-surgical diagnosis during imaging studies is very problematic and is due to the heterogeneous characteristics of the lesion in imaging, with overlapping features of HCC and CCA. The predominant histological subtype within the lesion establishes the predominant imaging findings. Therefore, in this scenario, the radiological findings characteristic of HCC show an overlap with those of CCA. Since cHCC-CCAs are prevalent in patients at high risk of HCC and there is a risk that these may mimic HCC, it is currently difficult to see a non-invasive diagnosis of HCC. Surgery is the only curative treatment of HCC-CCA. The role of liver transplantation (LT) in the treatment of cHCC-CCA remains controversial, as is the role of ablative or systemic therapies in the treatment of this tumour. These lesions still remain challenging, both in diagnosis and in the treatment phase. Therefore, a pre-treatment imaging diagnosis is essential, as well as the identification of prognostic factors that could stratify the risk of recurrence and the most adequate therapy according to patient characteristics.

Keywords: cHCC-CCA; diagnosis; MRI; CT; LI-RADS; surgical resection; ablative treatment

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1. Introduction

Combined hepatocellular-cholangiocarcinoma (cHCC-CCA) is an unusual subtype of primary liver malignancy, with an incidence that varies among different reports between

0.4 and 14.2% of all primitive hepatic cancers [1–5]. In the literature, it has been known by several terminologies, including mixed hepatocellular carcinomacholangiocarcinoma (HCC-CC), hybrid HCC-CC, or combined liver and bile duct carcinoma [6,7].

Among the risk factors, hepatitis B and hepatitis C virus infections, cirrhosis, and male gender are widely reported [8–16]. cHCC-CC is usually thought of as an aggressive tumour mainly due to its poor prognosis. This feature is also correlated to an erratum diagnosis during pre-surgical radiological studies, when the lesion is classified as an hepatocellular carcinoma (HCC) or intrahepatic mass-forming cholangiocarcinoma (iCCA) [17–23].

This study is a narrative review of the current knowledge of clinical features, pathology assessment, diagnosis, and treatment of cHCC-CCA.

2. Pathology Assessment

Histologically, cHCC-CCA is characterised by 2 distinct morphological patterns: HCC and intrahepatic CCA (iCCA) [24–28].

HCC-CCA's first classification was developed by Allen and Lisa in 1949 [29]. They classified HCC-CC into 3 types:

- Type A: HCC and CCA are present at different sites in the same liver;
- Type B: HCC and iCCA are present at adjacent sites;
- Type C: HCC and iCCA are combined within the same tumour.

In 1985, Goodman et al., in a review of 24 cases of this tumour, described three different histologic types [30]. Type I or "collision tumour" was characterized by the presence of both HCC and iCCA in the same patient. Type II or "transitional tumour" was characterized by the presence of the same lesions in an area with intermediate differentiation between HCC and iCCA. Type III or "fibrolamellar tumour" resembled the HCC fibrolamellar, also containing mucin-producing pseudoglands. Type III differs from the others since it is typical in younger patients, who do not have cirrhosis [26].

The World Health Organization (WHO) introduced in 2010 the last classification system, which divides cHCC-CCA into two types: classical type (a single tumour with both differentiations) and cHCC-CC with stem cell features [31]. This last one can be sub-classified into three variants: "typical", "intermediate cell", and "cholangiolocellular" subtypes. Recently, it has been demonstrated that the "stem cell" subtype can be proven in different types of hepatic tumours [32–35].

All primary liver cancer subtypes can be combined in the same nodule, and when it occurs, a precise description and percentage of each cancer type present in surgical specimens are recommended [36,37].

3. Epidemiology, Clinical Features, and Risks Factors

Nowadays, there is no clear profile of the patients affected by this rare primary hepatic neoplasm, being highly dependent on the geographic region. Indeed, the etiology and risk factors for this cancer may differ between different regions in the East and West. This reflects the different prevalence of risk factors in different countries. One-quarter of the global population is estimated to have non-alcoholic fatty liver disease (NAFLD). NAFLD is already the fastest-growing cause of HCC in the USA, France, and the UK. Globally, the prevalence of NAFLD-related HCC is likely to increase concomitantly with the growing obesity epidemic. The estimated annual incidence of HCC ranges from 0.5% to 2.6% among patients with NASH cirrhosis. The incidence of HCC among patients with non-cirrhotic NAFLD is lower, approximately 0.1 to 1.3 per 1000 patient-years. Although the incidence of NAFLD-related HCC is lower than that of HCC of other aetiologies, such as hepatitis C, more people have NAFLD than other liver diseases [38]. Chronic liver damage and subsequent liver cirrhosis are strong oncogenic factors [39]. Several studies have highlighted risk factors such as male gender, cirrhosis, hepatitis infection, family history of liver cancer, heavy alcohol consumption, and diabetes mellitus [40,41]. In Asian studies, the high man: woman ratio and prevalence of virus B infection in cHCC-CCA patients are similar to HCC patients compared to iCC patients [40–42]. Otherwise, in Western

reports, there is a lesser male predominance and a lower prevalence of virus B infection compared to virus C infection [43]. Furthermore, several researchers have described that cHCC-CCA has a poor prognosis and more aggressive behavior compared to HCC and/or iCCA alone [44,45].

The clinical appearance of cHCC-CCA is analogous to that of HCC and iCCA. In fact, it has usually nonspecific symptoms characterized by fatigue, abdominal pain, weight loss, pruritus, and, in advanced states, jaundice, ascites, acute cholangitis, and hepatomegaly [46]. Additionally, in cHCC-CCA patients, it is possible to find several tumour markers, such as alpha-fetoprotein, carcinoembryonic antigen, and carbohydrate antigen 19.9 [47–49]. Although these biomarkers are not specific to cHCC-CCA and may be found even in non-oncological disorders, an increase in their levels should be investigated [50].

4. Diagnosis

Diagnosis of cHCC-CCA is mainly based on histology from biopsies or surgical specimens [51,52]. Liver biopsy had an estimated sensitivity of 48% and specificity of 100% for the diagnosis of cHCC-CCA in the pre-surgical setting [53].

A correct pre-surgical diagnosis during imaging studies is very problematic due to the heterogeneous characteristics of the lesion in imaging, with overlapping features of HCC and CCA (Figure 1) [54–65]. The predominant histological subtype within the lesion establishes the predominant imaging findings. Therefore, in this scenario, the radiological findings characteristic of HCC show an overlap with those of CCA. Since cHCC-CCAs are prevalent in patients with high-risk HCC and there is the risk that these may mimic HCC, it is difficult currently to see a non-invasive diagnosis of HCC [66–70]. Current imaging-based criteria for HCC diagnosis have been grouped into Liver Imaging Reporting and Data System (LI-RADS), which is a scheme for interpreting and reporting imaging features in computed tomography (CT) and magnetic resonance (MR) studies in patients at risk of HCC [71–76]. In LI-RADS, key imaging features and ancillary features are evaluated, and diagnosis is due to the presence of the major features that are used to classify LI-RADS-category 3 (LR-3), LI-RADS-category 4 (LR-4), and LI-RADS-category 5 (LR-5), including arterial phase hyper potentiation, tumour diameter, washout, capsule appearance, and threshold growth. Ancillary features that aid in the HCC diagnosis include lesion signal hypointensity during the hepatobiliary phase of an MR contrast study with a liver-specific contrast agent, transitional phase hypointensity, mild to moderate signal hyperintensity in T2-W sequences, restricted diffusion, mosaic architecture, nodule architecture in the nodule, intralesional fat, lesional iron, or fat sparing, blood products, and a diameter increase that is less than the growth threshold [77–81]. Although vascular criteria are the main features that allow an accurate diagnosis, other data, such as restricted diffusion and the signal of T2-W sequences, could favor the characterization of the lesion. However, in the assessment of cHCC-CCA, when the predominant subtype is HCC, these data do not allow a proper diagnosis. On the other hand, for lesions with a predominant CCA component, characteristics that favor the diagnosis of LR-M category and the presence of satellite nodules (Figure 2) include hyperintense signal on T2-W, restricted diffusion, and the absence of capsule appearance in a nodule with peripheral and progressive contrast (Figure 3), should aid in the diagnosis of cHCC-CCA [77]. In addition, Granata et al. compared a control group of patients with a histological diagnosis of iCCA with cHCC-CCA and showed that T1 and T2-W signal intensity (SI), restricted diffusion, and transitional phase (TP) and hepatobiliary phase (HP) appearances allowed differentiation between mass-forming and mimicking ICCs with statistical significance, making MRI a valuable diagnostic tool for these lesions [7].

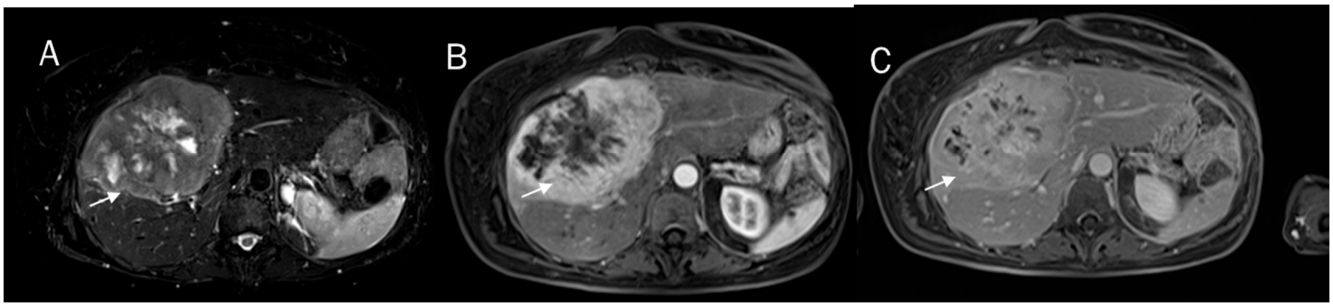

Figure 1. cHCC-CCA on IV-VIII hepatic segment. The lesion (arrow) shows the hyperintense signal on T2-W sequences (**A**) and progressive contrast enhancement during arterial (**B**) and venous (**C**) phases of contrast studies, features typical of iCCA.

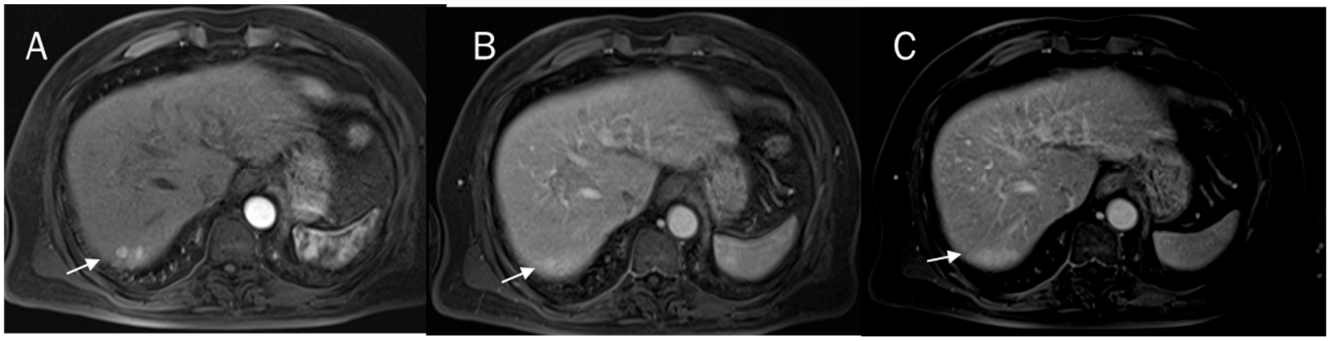

Figure 2. Satellite nodules (arrows) on VII hepatic segment with progressive contrast enhancement during the arterial (**A**), portal (**B**), and late (**C**) phases of contrast study.

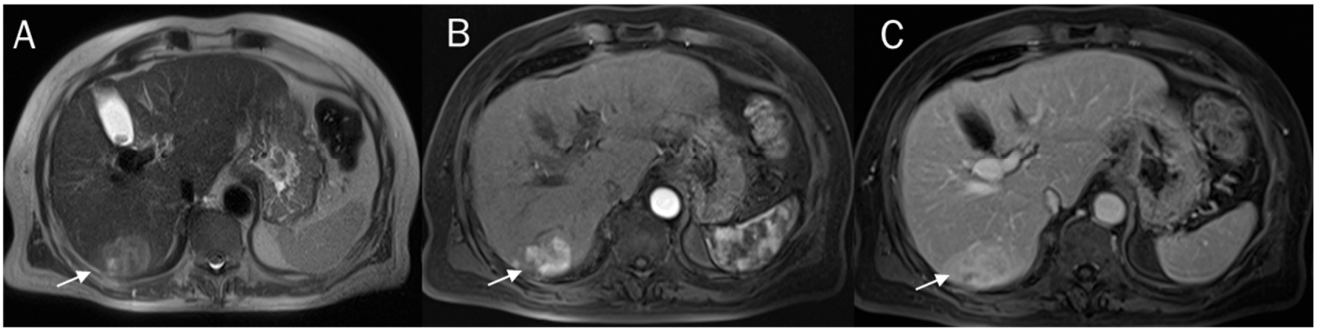

Figure 3. cHCC-CCA on VI hepatic segment. The lesion (arrows) shows hyperintense signal on T2-W sequences (**A**) and progressive contrast enhancement during the arterial (**B**) and venous (**C**) phases of contrast studies.

Considering the diagnostic criteria, the imaging modalities that should be chosen in cHCC-CCA assessment are CT and MRI.

A protocol CT study should comprise multiphase imaging with thin collimation, including non-contrast, arterial, portal or venous, and delayed phase images. The introduction of new techniques such as dual-energy CT (DECT) and perfusion CT [82–91] has increased the diagnostic performance of CT in the characterization of focal liver lesions [92,93].

MRI studies can be performed with a 1.5 T or 3 T system using an abdominal-phased array coil. An MRI liver study protocol should comprise multi-shot fast spin-echo T2-weighted (W) images, with and without fat suppression; T1-W with double-echo chemical shift; T1-W before and after contrast administration, including arterial, portal and late-phase; and Diffusion sequences. When employing a hepatospecific contrast agent, hepatobiliary phase imaging can also be performed [94].

Today, MRI is unique compared to CT and US since it allows only one study protocol to assess conventional data obtained by T2-W and T1-W sequences, with functional data obtained by DWI, DCE-MRI, and Blood sequences. In this scenario, MRI is not only problem-solving but the first tool that should be used in an oncological setting [95–125]. However, imaging shows low diagnostic performance on its own, with a sensitivity of only 48% and a specificity of 81%, although the combination of imaging and biopsy can improve sensitivity (60%) and specificity (82%) [126]. Moreover, imaging is critical to guide liver biopsy and perform tumour staging [127].

5. Treatment

5.1. Surgery

Surgery is the only curative treatment for cHCC-CCA (Figures 4 and 5) [128]. According to current principles for oncologic liver surgery, liver resection aims to remove the lesion with adequate margins and with sufficient liver remnant volume. This needs a multiparametric patient assessment for a correct evaluation of the lesion and functional liver status [129]. As demonstrated by the study of Ma et al., resection margin >10 mm has been correlated with protracted disease-free survival, since these resection margins allow eradication of satellite nodules and micro-tumours located in the same hepatic segment [130]. Several features could guide the surgical procedure, comprising liver functional status, patient general status, tumour size, localization, and vascular infiltration. As reported by Garancini et al. [131], aggressive surgical approaches were significantly correlated with prolonged survival with respect to non-surgical treatments ($p < 0.001$). Moreover, major hepatectomy for cHCC-CCA was associated with higher 5-year Overall Survival (OS) and Disease-Free Survival (DFS) rates with respect to minor hepatectomy [129]. Bearing in mind that the cHCC-CCA patient is a patient with cirrhosis, the degree of portal hypertension should be evaluated in surgical management since significant portal hypertension is an absolute contraindication to the main approaches [132]. Furthermore, the lymphatic pattern of tumour spread in cHCC-CCA requires routine hilar lymphadenectomy [133]. Also, transitional cHCC-CCA tends to infiltrate portal and hepatic veins as HCC and tends to invade lymph nodes as iCCA. Several studies [134,135] recommended liver resection with regional lymph node dissection to obtain oncological radicality in patients with transitional cHCC-CCA. However, it has not been demonstrated if lymphadenectomy improves the prognosis [136–138]. The need for routine lymphadenectomy should currently restrict the use of a laparoscopic approach only to centres with extensive expertise both in liver surgery and laparoscopy [139,140].

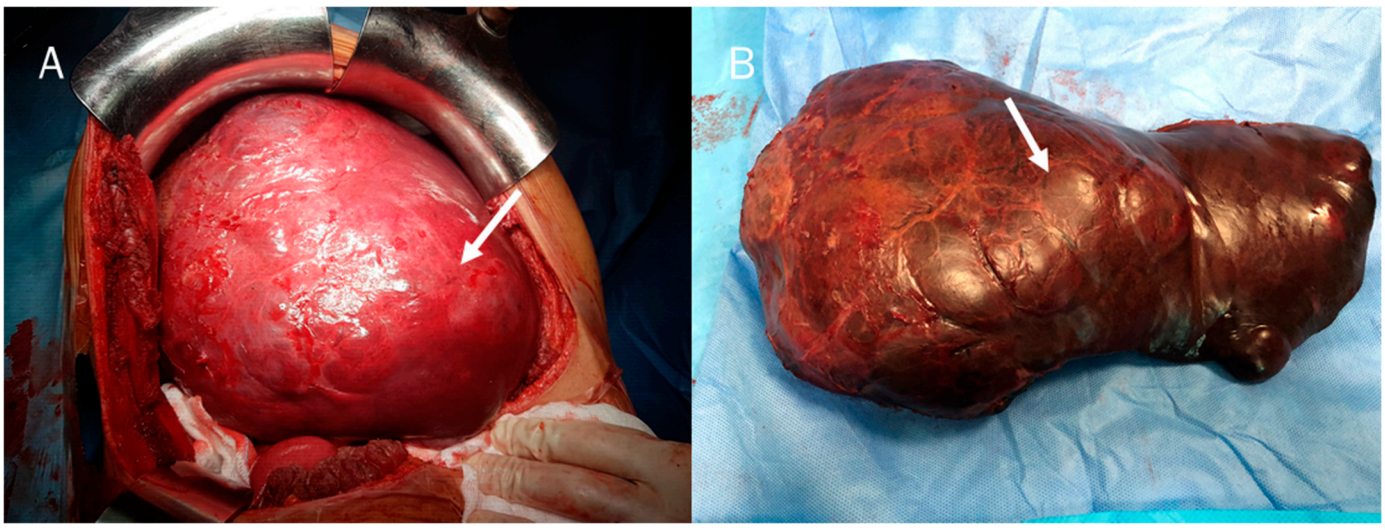

Figure 4. (**A**) cHCC-CCA during surgical resection (arrow); and (**B**) in surgical specimen (arrow).

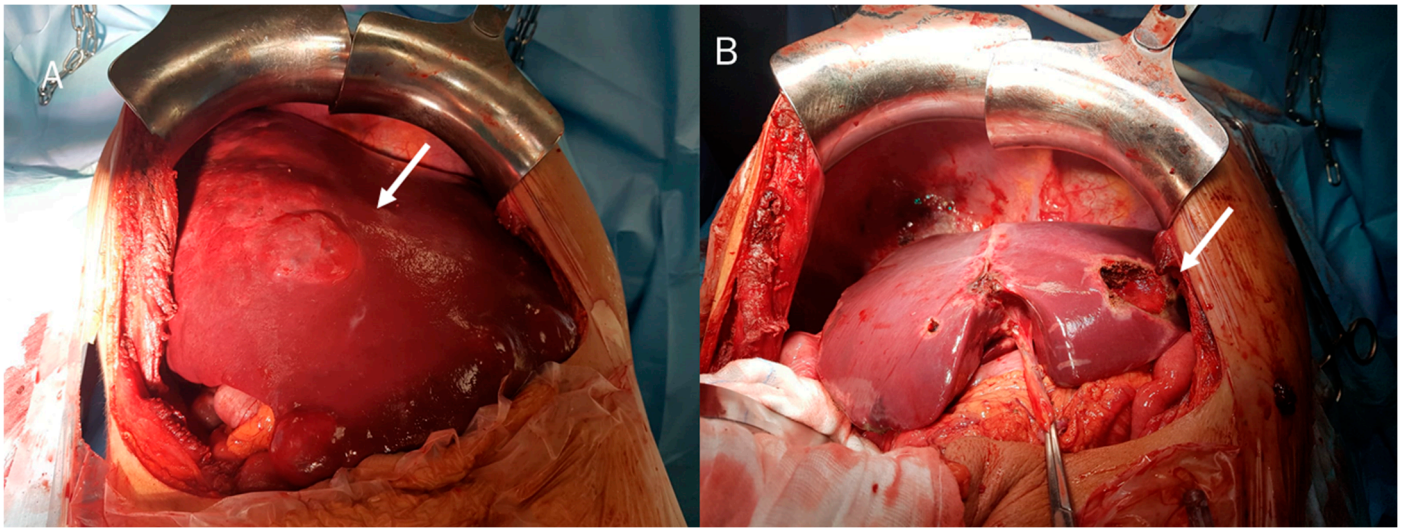

Figure 5. (**A**) cHCC-CCA on II hepatic segment during surgical resection (arrow); and (**B**) post-surgical resection features (arrow).

5.2. Liver Transplantation

The role of liver transplantation (LT) in the treatment of cHCC-CCA remains controversial. As with iCCAs, cHCC-CCA is a contraindication to liver transplantation due to historically high recurrence rates and poor OS. [141]. Several retrospective studies have assessed outcome for cHCC-CCA patients subjected to LT, reporting a recurrence rate of 40% [9,142–144]. However, due to the sample size analysed, the recurrence risk status post-LT remains problematic to evaluate. A systematic review reported a median DFS of 14.2 months and a median OS of 37.1 months [144]. Sapisochin et al. [142], in their multicenter matched cohort analysis, identified 42 iCCA (15 with cHCC-CCA) patients over a 10-year period. Researchers compared these patients to within-Milan criteria, HCC-matched controls, showing similar 5-year OS (78% vs. 86%) and recurrence risk (7% vs. 4%). However, these results correlate to the sample size assessed and lesser-advanced disease on the explant liver as compared to other published results. In addition, surveillance for this group was short, so data on disease stability over time are not available.

Lunsford et al. [145] conducted a propensity-matched analysis, within liver transplant recipients diagnosed with cHCC-CCA at explant (n = 12) were matched by pre- and post-transplant tumour characteristics 1:3 to patients with HCC (n = 36). cHCC-CCA tumours were more likely to be poorly differentiated and of a higher grade. When matched by pre-transplant characteristics, OS and RFS were inferior for cHCC-CCA, but the results were not statistically significant. When patients were compared by explant pathological criteria (diameter, differentiation, grade, and vascular invasion), recurrence rates remained minimally elevated for cHCC-CCA, but OS and RFS equalized (42% vs. 48% and 42% vs. 44%, at five years, respectively) [145]. All recurrences were found in patients with poorly differentiated lesions, with no patients having well- or moderately-differentiated tumours. These data favour the thesis that well- or moderately-differentiated cHCC-CCA patients could take advantage of LT.

5.3. Locoregional Treatments

Few studies have analysed the effectiveness of transarterial chemoembolization (TACE) on cHCC-CCA. Kim et al. [146], from 1997 to 2009, recruited 50 patients with non-resectable cHCC-CCA. TACE produced a partial response or stable disease in 70% of patients, essentially in tumours with APHE (feature typical of HCC predominant subtype), with a median OS of 12.3 months. Better outcomes were reported in patients treated with TACE for recurrence after the surgical approach [147,148]. cHCC-CCA with global enhancement

showed a significantly better response rate (complete remission + partial response) than the rim enhancement of the cHCC-CCA group (36% vs. 0%, $p = 0.005$), and it was comparable to that of the HCC-control group (35.6%, $p = 0.97$).

Data on radio-embolization (selective internal radiation therapy (SIRT)) and chemotherapy for non-resectable iCCA show that 22% of patients can be downstaged for surgical resection [149]. In the study by Malone et al., SIRT was associated with a 55% radiological response rate (15% complete response, 40% partial response), a 65% disease control rate, and a median OS of 9.3 months in 21 patients, suggesting a possible role for SIRT in locoregional control of cHCC-CCA [150]. However, since little data are currently available in the literature, more studies are necessary to establish the correct role of ablation treatments in cHCC-CCA patients.

5.4. Systemic Treatments

Today, the data reported on cHCC-CCA patients unfit for surgery are restricted to retrospective analyses, evaluating the first-line therapies authorised for HCC (sorafenib) and iCCA (gemcitabine/platinum regimens) [151–156].

Kobayashi et al., in a multicentre retrospective analysis of systemic chemotherapy for unresectable cHCC-CCA, enrolled 36 patients: 12 patients underwent first-line chemotherapy consisting of gemcitabine/cisplatin, 11 with fluorouracil/cisplatin, 5 with sorafenib and 8 with others. A multivariate evaluation showed that the OS in the sorafenib monotherapy group was poor with respect to the platinum-containing regimens group. The authors concluded that the platinum-containing regimen had more favorable outcomes than the sorafenib treatment [153]. Salimon et al., in a multicentric study that included 30 patients with unresectable cHCC-CCA, showed that gemcitabine plus platinum is effective as a first-line treatment of advanced cHCC-CCA [154]. Similar results were found in a monocentric study of 68 patients with unresectable cHCC-CCA [155]. In a recent retrospective analysis of 99 cHCC-CCA patients, researchers compared a group of patients (n = 67) who received sorafenib with those who received cytotoxic chemotherapy. Among the two groups (sorafenib vs. cytotoxic chemotherapy), outcomes were not significantly different (ORR, 9.7% vs. 21.6%, $p = 0.14$; median PFS, 4.2 vs. 2.9 months, $p = 0.52$; median OS, 10.7 vs. 10.6 months, $p = 0.34$) [156].

A better understanding of the molecular basis of cancer would help develop targeted therapeutic agents against the druggable genetic aberrations identified in cancer genomes [157–159]. Tyrosine kinase inhibitors (TKIs) that target anaplastic lymphoma kinase (ALK) are particularly effective in the treatment of a distinct subset of lung adenocarcinoma carrying ALK fusions. FIG- ROS1, the first identified targetable fusion kinase in CC, has so far been reported in two patients. Very recently, a novel kinase fusion, FGFR2-BICC1, was detected in two CC cases [157]. FGFR2 fusions occur in 13.6% of intrahepatic cholangiocarcinoma cases. The expression pattern of these fusions in association with sensitivity to FGFR inhibitors warrants a new molecular classification of cholangiocarcinoma and suggests a new therapeutic approach to the disease [157].

5.5. Conclusions

Although cHCC-CCA represents a rare entity, this tumour remains challenging both in diagnosis and treatment. Therefore, a pre-treatment imaging diagnosis is essential, as well as the identification of prognostic factors that could stratify the recurrence risk and the most adequate therapy according to patient characteristics.

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