# Chapter 3
# Biphenotypic Tumors


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## Epidemiology of Combined HCC-CCA

Primary liver cancer is broadly recognized as a spectrum marked by hepatocellular carcinoma (HCC) at one end, intrahepatic cholangiocarcinoma (iCCA) at the other end, and biphenotypic or combined hepatocellular-cholangiocarcinoma (cHCC-CCA) in the middle [1]. Classical HCC demonstrates hepatocytic differentiation while the CCA shows cholangiocytic differentiation. Primary liver cancers with features of both hepatocytic and cholangiocytic differentiation that do not completely fit cytologically or architecturally into either the HCC or CCA category have been broadly categorized as "mixed" or "combined" HCC-CCA. They have also been called "biphenotypic" primary liver cancers, combined liver and bile duct carcinoma, or hepato-cholangiocarcinoma [2, 3]. The term "collision tumor" is discouraged.

The most recent edition of the World Health Organization (WHO) classification of tumors of the digestive system defines cHCC-CCA as a tumor composed of an unequivocal mixture of both HCC and CCA [4]. They should have two distinct morphologies evident on the Hematoxylin and Eosin (H&E) stain, one of HCC and

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one of CCA. The two components can be found as adjacent nodules or areas within the same tumor, sometimes even with a transition zone.

The first case of a biphenotypic hepatic tumor was reported in 1903 [5]. The frequency of cHCC-CCA is about 1–6% of all primary liver cancers [6–10]. Patients with cHCC-CCA have a similar median age (of 62 years) compared with HCC (median age of 61 years) but are younger than those with CCA (median age 67 years) [11]. cHCC-CCA is seen more frequently in males than females [11]. The overall risk factors for cHCC-CCA are similar to those of conventional HCC such as viral hepatitis B and C as well as cirrhosis of any cause.

## Pathology of Combined HCC-CCA

cHCC-CCA tumors can develop in both cirrhotic and non-cirrhotic livers [7, 10, 12]. Approximately 80% are unifocal while 20% are multifocal [8, 13–15]. Most cHCC-CCA tumors measure between 5 and 10 cm in greatest dimension at the time of diagnosis [11]. A diagnosis of cHCC-CCA requires that both the HCC and CCA components are present in one nodule or in immediately adjacent nodules. Cases in which the liver shows HCC and CCA but in clearly separate nodules with intervening normal liver should be classified as double primaries and not as cHCC-CCA.

cHCC-CCA tumors must show the two distinct HCC and CCA morphologies on the H&E stained sections. Morphological features of HCC include the presence of trabecular or pseudo-acinar architecture with neoplastic cells showing similarity to normal liver cells up to a variable extent (hepatocytic differentiation) (Fig. 3.1a). Bile production may also be seen within this component. Features of CCA include acinar or glandular architecture similar to an adenocarcinoma, often with a desmoplastic stromal reaction (Fig. 3.1b). The two components may be intermixed or may be seen in separate regions of the same tumor. There are no published consensus guidelines for the minimum proportions of HCC or CCA to make the diagnosis of cHCC-CCA on either biopsy or resection specimens [16]. A recent study has shown that recurrent and/or metastatic cHCC-CCA can show a wide range of histomorphological patterns, replicating the heterogeneity of the primary tumor [17]. The originally minute foci of divergent differentiation in the primary tumor can become predominant later on. Hence, histological comparison between the primary liver tumor and their metastatic deposits can be informative and should be included in the management of patients with metastatic cHCC-CCA.

Special stains should be used only to confirm the H&E impression. The HCC component is positive for typical markers of hepatocellular differentiation such as HepPar1, arginase-1, and glypican 3 (Fig. 3.1c, d). The CCA is positive for biliary type keratins such as CK7 and CK19 and negative for markers of hepatocellular differentiation (Fig. 3.1e, f). Mucin production may also be seen in the CCA but is not a requirement. A diagnosis of cHCC-CCA should not be based on immunohistochemical findings only, without morphological correlation. The diagnosis of cHCC-CCA can be challenging on a needle core biopsy as it depends on the area of

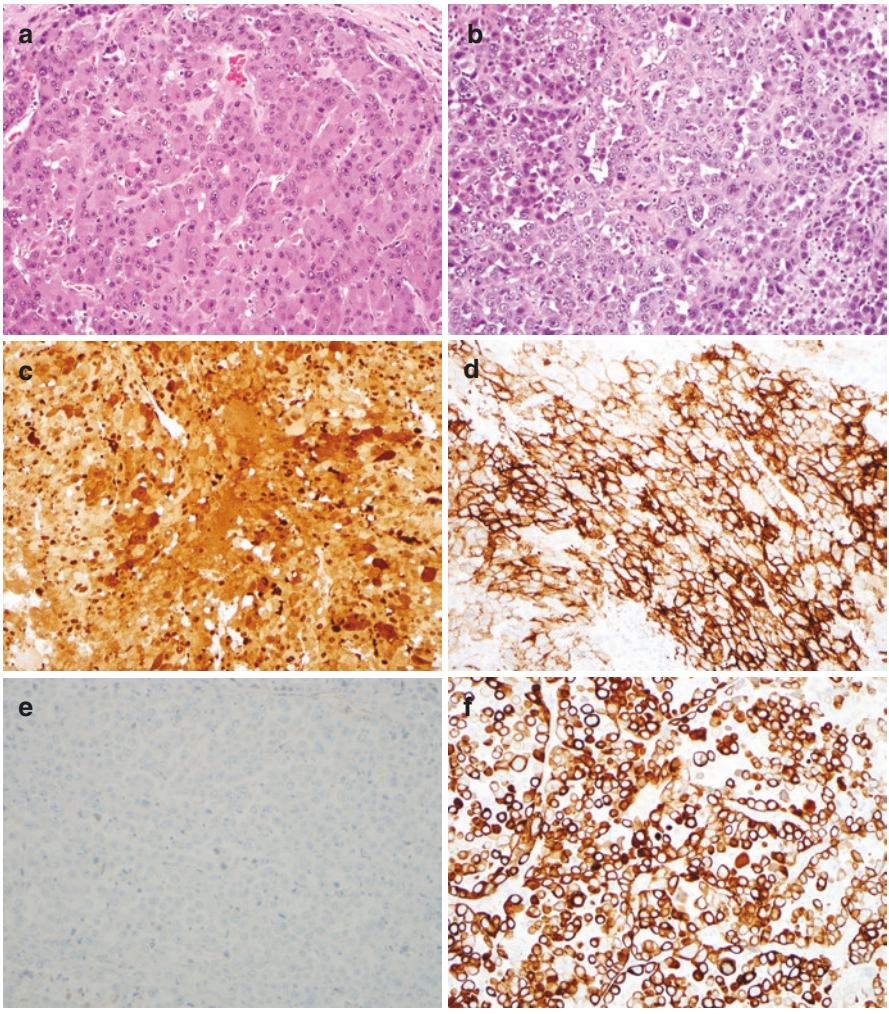


**Fig. 3.1** Histology of biphenotypic tumor. Hepatocellular carcinoma component showing trabecular arrangement of the tumor cells with typical hepatocellular carcinoma morphology (**a**). Cholangiocarcinoma component within the same tumor showing a glandular architecture (**b**). Arginase-1 immunostain showing positivity within the hepatocellular carcinoma component of the tumor (**c**). Glypican-3 immunostain is also positive within the hepatocellular carcinoma component of the tumor (**d**). Arginase-1 immunostain is negative within the cholangiocarcinoma component (**e**). Cytokeratin 7 immunostain is positive within the cholangiocarcinoma component (**f**)

the tumor sampled [18]. The true histopathology may only be confirmed after the evaluation of a resected surgical specimen. This clearly may create difficulties in the evaluation of unresectable cHCC-CCAs.

The current WHO classification divides cHCC-CCA into two subcategories: classic cHCC-CCA and cHCC-CCA with stem cell features when morphological

and/or immunophenotypical features of stem/progenitor cells predominate within the tumor [4]. The stem cell type is further subdivided into three subtypes, namely, typical subtype, intermediate–cell subtype, and cholangiolocellular subtype. The first two subtypes are associated with areas of hepatic differentiation, whereas the cholangiolocellular subtype shows CCA differentiation. Dense intratumoral fibrosis is a common finding in all subtypes. However, recent work has shown that stem cell phenotypes can be seen in other forms of primary liver cancers and hence these different WHO categories are not clearly separable [19, 20]. It is also now recommended that there should no longer be formal diagnostic subtypes of cHCC-CCA based on the identification of stem/progenitor cells [16].

Molecular studies, although limited in number, have highlighted significant heterogeneity within these tumors [21–23]. A stem cell that differentiates into both hepatocytes and bile duct epithelial cells is suspected to be the cell of origin for these tumors [24–28]. Molecular studies have shown that cHCC-CCA shares some traits with HCC and others with CCA, supporting its status as a distinct entity [21, 29–31].

The reported 3-year and 5-year overall survival rates range between 11–47% and 10–40% for cHCC-CCA [3]. Its prognosis falls in between that of CCA and HCC and is reportedly worse than that of conventional HCC [9]. A recent retrospective review of the National Cancer Data Base (NCDB) showed the unadjusted median overall survival for cHCC-CCA to be 7.9 months [11]. Some studies have shown the overall prognosis of cHCC-CCA to be similar to that of CCA, but this is debatable as other studies have shown variable outcomes [9, 13, 32]. cHCC-CCA has a higher rate of recurrence after resection and liver transplantation [33, 34]. In the recent 8th edition AJCC staging system, cHCC-CCA is staged using the CCA protocol [35]. This is not unreasonable as the CCA component appears to drive the worse prognosis of these tumors.

## Imaging of Combined HCC-CCA

Combined HCC-CCA liver tumors contain cellular and architectural elements of both HCC and CCA. These lesions consequently have a spectrum of imaging appearances including lesions with typical imaging findings of HCC, some with an appearance typical of CCA, and others with a mixture of features. The dominant histologic component tends to determine the appearance of the mass at imaging [36–40].

Combined HCC-CCA tumors most commonly resemble intrahepatic mass-forming CCA or a metastasis at imaging [41]. These masses characteristically have the greatest cellularity at the periphery of the lesion and a fibrous component centrally, which may result in a targetoid appearance at cross-sectional imaging. The masses are hypoattenuating to background liver at computed tomography (CT) and T2 hyperintense and T1 hypointense at magnetic resonance imaging (MRI) [41]. At

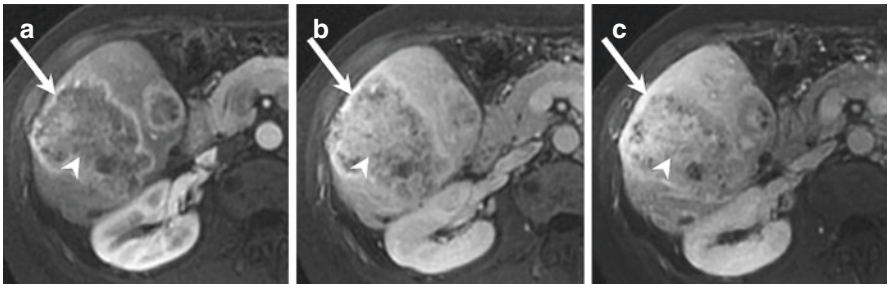


**Fig. 3.2** cHCC-CCA with imaging appearance resembling cholangiocarcinoma. (**a**) T1-weighted fat saturated MRI image demonstrates a mass with continuous peripheral late arterial hyperenhancement (arrow) and heterogenous hypointensity centrally (arrowhead). (**b**) Portal venous and (**c**) delayed phase images show the fade of the peripheral enhancement to near iso-intensity with the adjacent liver (**b**, **c**, arrows) and progressively increasing central enhancement (**b**, **c**, arrowheads)

dynamic contrast-enhanced CT or MRI, the peripheral portion of the tumor enhances in the late arterial or portal venous phase of imaging (Fig. 3.2). On subsequent phases the peripheral enhancement may fade to a degree similar to the surrounding parenchyma or may demonstrate a washout appearance and become hypoattenuating (CT) or hypointense (MRI). The central component initially enhances poorly in the late arterial phase, but as injected contrast material equilibrates to the extravascular, extracellular space, there is progressively greater enhancement in the delayed phases. Combined HCC-CCA cannot be reliably differentiated from CCA by imaging alone; however, imaging features reported to be suggestive of cHCC-CCA tumor in a mass which otherwise resembles CCA include: strong arterial phase enhancement, washout, lipid content, hemorrhage, and venous tumor thrombus [41, 42].

The cHCC-CCA tumors most likely to demonstrate an imaging pattern similar to HCC have a predominance of the HCC histologic subtype [36, 37, 39, 40, 43]. The tumors may demonstrate characteristic imaging findings of HCC, including late arterial phase hyperenhancement, portal venous and/or delayed phase washout, and capsule appearance (Fig. 3.3) [41]. These tumors may also have additional findings associated with HCC including mosaic architecture, lipid content, or venous invasion [44]. It has been reported that up to 30–40% of biphenotypic tumors may have an imaging appearance mimicking HCC, and prior studies have confirmed the difficulty in differentiating the two based on imaging [42, 45, 46]. This is particularly problematic for patients at risk for HCC in whom imaging criteria may be used to make a definitive diagnosis before instituting therapy. Tumors demonstrating enhancement features potentially representative of HCC by traditional OPTN criteria can be referred for inappropriate therapy, including transplant [41, 45]. Fortunately, many cHCC-CCA with enhancement characteristics similar to HCC will also demonstrate American College of Radiology, Liver Imaging and Reporting Data System (LIRADS) ancillary findings favoring non-HCC malignancy. These

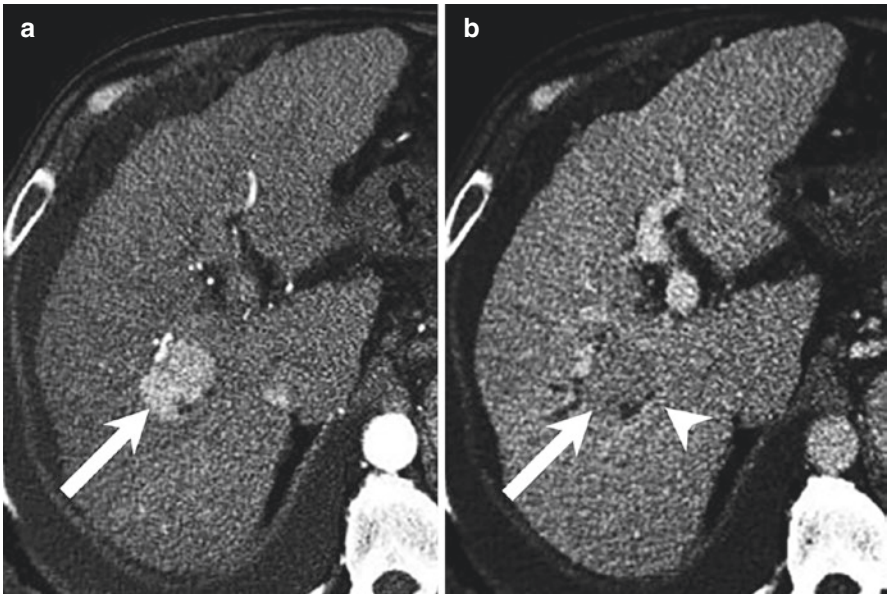


**Fig. 3.3** cHCC-CCA with imaging appearance resembling HCC. (**a**) Late arterial phase CT image demonstrates a homogenously hyperenhancing mass (arrow). (**b**) Portal venous phase image shows the lesion becoming hypoattenuating when compared with the adjacent liver (arrow) consistent with a washout appearance. A subtle hyperattenuating capsule appearance is also seen at the periphery of the lesion (arrowhead)

ancillary findings are important for maintaining specificity for the diagnosis of HCC, and they include: peripheral pattern of enhancement/washout, biliary obstruction out of proportion to size of the mass, progressive central enhancement, liver capsular retraction, or marked restricted diffusion [41, 45, 46].

Combined HCC-CCA may demonstrate imaging findings typical of CCA and HCC in separate regions within a single mass (Fig. 3.4). This imaging pattern is uncommon but is highly suggestive of a cHCC-CCA tumor. The imaging pattern must also be carefully scrutinized for evidence of a collision tumor, as HCC and CCA which originate separately within the same liver but grow into one another are not considered a cHCC-CCA by WHO criteria [47].

Ultrasound and positron emission tomography (PET) may also be used to evaluate cHCC-CCA tumors. A tumor may be initially discovered at ultrasound. Unfortunately, routine grayscale and Doppler ultrasound findings are not specific and are unable to diagnose a cHCC-CCA tumor [41]. Ultrasound may be helpful for identifying important secondary findings such as biliary ductal obstruction or vascular tumor thrombus. Limited information is available regarding the PET-CT features of cHCC-CCA [41, 48, 49]. PET-CT has a limited role in diagnosis of HCC and CCA due to variable lesion tracer activity and relatively high background liver activity [50, 51]. When imaged with F-18 labeled fluorodeoxyglucose, cHCC-CCA

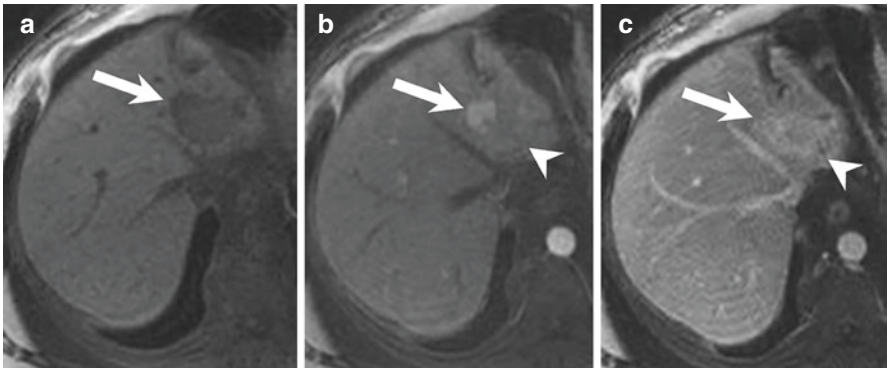


**Fig. 3.4** cHCC-CCA with mixed imaging features of both HCC and CCA. (**a**) Precontrast T1-weighted fat saturated MRI image shows a hypoattenuating hepatic lesion (arrow). (**b**) Late arterial phase image demonstrates a nodular region of hyperenhancement (arrow), while the larger portion of the tumor has become iso-attenuating when compared with the adjacent liver (arrowhead). (**c**) Delayed phase image shows subtle washout of the previously hyperenhancing component of the tumor (arrow). The remainder of the tumor has become progressively more intense (arrowhead)

tumors have been reported to demonstrate marked hypermetabolism with high standard uptake values. This suggests a possible role for PET-CT for initial diagnosis, staging, or follow-up after treatment.

A comparison of cross-sectional imaging findings with laboratory values may be helpful for diagnosis. Serum markers including C19-9, which is associated with cholangiocarcinoma and alpha fetoprotein (AFP), which is associated with HCC, can be a helpful adjunct to image interpretation when they are elevated. Combined HCC-CCA tumor should be included in the differential diagnosis when the cross-sectional imaging findings are consistent with hepatocellular carcinoma, but there is elevation of the serum CA 19-9. Conversely, imaging findings consistent with CCA or metastasis in the setting of an elevated AFP are also suggestive of a cHCC-CCA tumor.

## Management of Combined HCC-CCA

There are no clear guidelines with regard to the management of cHCC-CCA. As is the case with other malignancies of the liver, surgical resection is the only treatment offering the possibility of a cure. However, many patients present with disease too advanced for surgical management, and their disease is, given the paucity of any trials dedicated to the management specifically of cHCC-CCA, managed via therapeutic strategies utilized in the management of either HCC or ICC alone.

## *Surgery*

Surgical management strategies remain the sole modality associated with a possibility of cure for patients with cHCC-CCA. Eligibility for surgery in this unique population of patients hinges on a number of factors including underlying cirrhosis, the patient's general medical condition, tumor extent, and local anatomic conditions. Complete surgical excision with negative margins and limited impingement upon liver function is the ultimate goal of therapy. Severe liver dysfunction, of course, predicts a poor prognosis, regardless of the success of the actual procedure, and usually precludes resection.

In one series from a Western academic medical center, 78% of patients seen with cHCC-CCA were eligible for surgical resection [10]. This high proportion may have been due in part to referral bias, but nevertheless, it showed that many cHCC-CCAs may be eligible for resection with curative intent. cHCC-CCA tends to behave like HCC with respect to portal and hepatic venous infiltration and like CCA with regard to lymph node metastasis [52]. In autopsy studies, lymph node metastases have been observed in 76% of patients with cHCC-CCA [53]. Comparatively, lymph node metastases were present in only 30% of HCC patients and 69% of CCA patients [53]. Hence, hilar lymph node dissection is recommended as part of the surgical management of cHCC-CCA. However, the prognostic benefit of lymphadenectomy for cHCC-CCA remains controversial [54–57]. Also of significance and an open question for investigation is whether the addition of neoadjuvant or adjuvant systemic chemotherapy overall and, also more specifically, in patients undergoing lymph node dissection improves prognosis.

A unique consideration in the management of patients with liver cancers in general is that of the underlying liver disease. For cirrhotic patients, given their reduced functional reserve, hepatic resection has the potential for debilitating complications, so the adoption of strict selection criteria is imperative to avoid significant perioperative and overall morbidity and mortality due to post-operative liver decompensation [58].

Data regarding survival outcomes with non-transplant surgical management of cHCC-CCA has come mostly in the form of retrospective case series. Generally, 5-year overall survival has ranged between 24% and 31% while disease-free survival at 3 years ranges between 26% and 41% [59–62]. One study also carefully evaluated whether a difference in survival outcomes existed based on the predominance of the CCA component and found no such difference [59]. Differences in outcomes have also been evaluated among the three liver malignancies (HCC, cHCC-CCA, and CCA), and it has been noted that post-resection tumor recurrence rates do not differ significantly, whereas differences in survival rates have been significant, with a median survival after tumor recurrence of 51, 8, and 6 months, respectively, reflecting the general propensity of cHCC-CCA to behave in a similar manner to CCA [60].

## *Liver Transplantation*

The role of liver transplantation in the treatment of HCC is well established as an effective option for patients with HCC, generally guided by the Milan criteria [63]. Contrary to this, the role of transplantation for cHCC-CCA is undefined and controversial at this time, primarily because of the high rate of tumor recurrence and variable survival outcomes [64, 65].

Data regarding survival outcomes of cHCC-CCA patients treated with liver transplantation is limited and has come mostly in the form of retrospective studies. Overall, 3- and 5-year overall survival rates reported in the existing literature have ranged between 39–78% and 16–78%, respectively [8, 61, 66–70]. Disease free survival at 3 and 5 years in the existing literature has ranged between 30–47% and 28–45%, respectively [61, 69–71]. Recurrence rates within 5 years of transplant have ranged between 32% and 60% [71–73].

To come to a consensus on the role of transplant for cHCC-CCA, comparing outcomes to those of transplant for HCC has been done in a number of studies, though most have been small single institution studies. Lunsford et al. sought to compare post-transplant oncologic outcomes for cHCC-CCA to a matched cohort of HCC liver transplant recipients in a retrospective, single-center analysis of 12 patients with cHCC-CCA diagnosed on explant pathology. When matched to an HCC cohort with similar explant pathology, cHCC-CCA had similar 5-year disease-free survival (42% vs 44%, $P = 0.45$) but trended toward higher post-transplant recurrence (50% vs 27%, $P = 0.13$) [71]. Another study evaluated 42 patients undergoing a transplant for HCC but with a diagnosis of cHCC-CCA or iCCA on pathologic evaluation. Compared to a control group of 84 patients with HCC, no differences in 1-, 3-, and 5-year actuarial survival rates were observed between the cHCC-CCA subgroup and the HCC controls [67]. Another group reported their experience with living donor liver transplantation for cHCC-CCA from a cohort of 710 patients at a single institution. Of this group, 377 of them received transplantation for HCC and 11 patients were diagnosed with cHCC-CCA pathologically in the explant livers. Outcomes for patients with cHCC-CCA undergoing transplant were worse than outcomes for those with HCC [69]. The Mayo Clinic group also retrospectively reviewed their experience in 12 patients with a finding of cHCC-CCA post-transplant. They noted that 5-year survival was comparable to or better than liver transplantation for iCCA, but poorer than for HCC patients who met the Milan criteria [66]. In a departure from other studies, Vilchez and colleagues utilized data from a much bigger sample size, 4049 patients in the United Network for Organ Sharing (UNOS) database, to compare outcomes in patients undergoing liver transplantation for cHCC-CCA versus patients with HCC or iCCA in a retrospective analysis. Of this group 94 had cHCC-CCA, 3515 HCC, and 440 iCCA. Overall survival rates at 1, 3 and 5 years for cHCC-CCA were similar to the rates for iCCA, but significantly worse than for HCC [74].

Comparisons of outcomes with resection versus liver transplantation for cHCC-CCA have also been carried out, but again, the data is sparse and

conflicting. Jung et al. evaluated the long-term outcomes following liver transplantation and hepatic resection for cHCC-CCA in 32 patients. Tumor recurrence and survival rates did not differ significantly between the transplant and resection groups [73]. Groeschl et al. questioned the benefit of transplantation, compared with resection, for patients with cHCC-CCA and evaluated a much larger sample size, 3378 patients, with localized HCC or cHCC-CCA treated with surgical resection or transplant identified using the Surveillance, Epidemiology, and End Results (SEER) database. Of this group, 43% received liver transplants and 57% resection, including 54 patients with cHCC-CCA, of whom 35% were transplanted and 65% resected. Transplantation for localized cHCC-CCA conferred a survival benefit similar to liver resection for cHCC-CCA. Patients undergoing resection of HCC and cHCC-CCA had similar 3-year overall survival; however 3-year overall survival for patients undergoing transplant was significantly greater for HCC (78%) than for cHCC-CCA (48%) [8]. These results suggest that cHCC-CCA generally have more aggressive biology and worse outcomes than HCC, with outcomes that are more similar to the outcomes for iCCA. However, the generation of additional robust data evaluating liver transplantation in the management of cHCC-CCA is an area of unmet clinical need.

## *Locoregional Therapies*

Locoregional treatments, such as transarterial chemoembolization and radioembolization, are some of the most widely used treatments for HCC [75, 76]. Data for the outcomes of these embolic therapies in the management of cHCC-CCA is lacking, however. cHCC-CCA tumors with a substantial CCA component may be less vascular and more fibrotic than HCC and thus may be less responsive to embolic therapies. Chan et al. demonstrated radioembolization to be a safe and promising treatment option, albeit in a small cohort of patients. Patients with histopathologically confirmed cHCC-CCA treated with radioembolization were retrospectively evaluated. Ten patients with unresectable cHCC-CCA underwent 14 radioembolization treatments with resin ($n = 6$) or glass ($n = 4$ patients) microspheres. Clinical toxicities were limited to grade 1–2 fatigue, anorexia, nausea, or abdominal pain. Median overall survival from the first radioembolization treatment and from initial diagnosis was 10.2 and 17.7 months, respectively. Best radiological response was 60% partial response and 40% stable disease by mRECIST criteria [77].

Ablation-based treatments are also a possible option for the treatment of disease recurrence in select patients [78]. Patients who are unresectable due to locally advanced disease or those with local recurrence may also be candidates for palliative stereotactic body radiation therapy with or without concomitant chemotherapy. Symptomatic and local tumor control has been reported with such treatment [52, 79].

### *Systemic Therapy*

For those patients with advanced disease, systemic chemotherapy may be an option. However, there is no clear standard therapeutic strategy or regimen for the management of this cohort of patients with cHCC-CCA. Additionally, response rates reported thus far have been low [80–82]. Recently, data reporting experiences with systemic therapy have provided more updated outcomes data with newer therapeutics. One group reported on 39 cases of recurrent unresectable or metastatic cHCC-CCA. In 28 patients, first-line systemic therapy included: gemcitabine or 5-fluorouracil monotherapy (18%), chemotherapy (43%), sorafenib (29%), or clinical trials (11%). Six patients who received chemotherapy also received sorafenib. The median progression free survival (PFS) and overall survival (OS) from the time of first systemic treatment were 2.4 and 10 months, respectively. The median PFS for monotherapy, sorafenib, chemotherapy, and chemotherapy + sorafenib were 1.8, 3.1, 4.5, and 8.2 months, respectively. Overall survival favored chemotherapy + sorafenib with median OS of 1.8, 7.6, 8.4, and 14.7 months (Log rank $p = 0.01$), respectively [81]. Rogers et al. reported on 7 patients who received first-line sorafenib (3 patients), gemcitabine plus bevacizumab (2 patients), gemcitabine alone (1 patient), and gemcitabine plus cisplatin (1 patient). Progressive disease at first reimaging was seen in 71% of patients. Front-line treatment showed a median PFS of just 3.4 months. Of the 3 patients who received second-line therapy, a median PFS of 6.5 months was noted with regimens such as gemcitabine plus oxaliplatin (1 patient), gemcitabine plus oxaliplatin plus bevacizumab (1 patient), and fluorouracil plus leucovorin plus irinotecan (FOLFIRI) (1 patient). The group concluded, albeit in this small cohort, that all patients who received a platinum (cisplatin or oxaliplatin) in combination with gemcitabine during their disease course showed disease control and an impressive median OS of 11.7 months, compared with a median OS for the entire cohort of 8.3 months, regardless of the timing of the therapy [83].

In the era of genomics and precision medicine, with novel therapies being approved for HCC and with significant strides made in therapeutically important genomic subtyping of cholangiocarcinoma in recent years, an understanding of the unique molecular profile underpinning the pathogenesis of cHCC-CCA is critical. Such information is generally lacking thus far. One study sought to identify genetic and gene expression alterations in cHCC-CCA versus iCCA in a Chinese population. Analyses were performed on 10 iCCA and 10 cHCC-CCA samples, each controlled by matched adjacent non-tumor liver tissue, and the results compared with datasets from The Cancer Genome Atlas (TCGA) project. Differences in mutational and transcriptional landscapes of cHCC-CCA and iCCA were clearly delineated [23]. Sasaki et al. specifically examined the mutational statuses of KRAS, IDH1 or IDH2 (IDH1/2), ARID1A, the TERT promoter, and TP53 and their relationships with clinicopathological features in 53 patients with cHCC-CCA. Mutations in TP53, the TERT promoter, ARID1A, IDH1/2, and KRAS were detected in 45.3%, 31.3%, 13.2%, 11.8%, and 7.5% of patients, respectively. TP53 mutations correlated with α-fetoprotein (AFP) positivity. TERT promoter mutations correlated with

hepatitis B etiology, female-predominance, an intermediate subtype-predominant histology, higher clinical stage, the presence of lymph node metastases, and previous therapy. ARID1A mutations correlated with alcoholic liver disease, smaller tumor size, a lower grade of coexistent HCC, and AFP positivity and were also associated with cholangiolocellular carcinoma subtype predominance. KRAS mutations correlated with high histological diversity scores and the presence of distant metastasis [84]. These initial observations suggest that there may be an opportunity to molecularly subclassify cHCC-CCA in a manner that allows better prediction of response to specific therapies and clinical outcomes.

Overall, with significant advances being made in the management of both HCC and iCCA and with advances in our ability to investigate the genomic changes underlying these diseases, our understanding of cHCC-CCA as a distinct entity is sure to grow and this should expand the repertoire of therapeutic options for patients with cHCC-CCA.

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