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New insights in physiopathology and clinical care of rare primary liver cancers

Elia Gigante^{1,2,7}, Valérie Paradis^{2,3,6}, Maxime Ronot^{2,4,6}, François Cauchy^{2,5,6}, Olivier Soubrane^{2,5,6}, Nathalie Ganne-Carrié^{1,7,8}, Jean-Charles Nault^{1,7,8}

- 1) Service d'hépatologie, Hôpital Jean Verdier, Hôpitaux Universitaires Paris-Seine-Saint-Denis, Assistance-Publique Hôpitaux de Paris, Bondy, France.
- 2) Centre de recherche sur l'inflammation, Inserm, Université de Paris, INSERM UMR 1149 « De l'inflammation au cancer », Paris, France
- 3) Service d'anatomie pathologique, Hôpitaux Universitaires Paris-Nord-Val-de-Seine, Assistance-Publique Hôpitaux de Paris, Clichy, France
- 4) Service de radiologie, Hôpital Beaujon, Hôpitaux Universitaires Paris-Nord-Val-de-Seine, Assistance-Publique Hôpitaux de Paris, Clichy, France
- 5) Service de chirurgie hépato-bilio-pancréatique et transplantation hépatique, Hôpitaux Universitaires Paris-Nord-Val-de-Seine, Assistance-Publique Hôpitaux de Paris, Clichy, France
- 6) Université de Paris, Paris, France
- 7) Unité de Formation et de Recherche Santé Médecine et Biologie Humaine, Université Paris 13, Paris, France
- 8) Centre de Recherche des Cordeliers, Inserm, Sorbonne Université, Université Paris, INSERM UMR 1138, Functional Genomics of Solid Tumors, F-75006, Paris, France

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List of abbreviations:

Combined hepato-cholangiocarcinoma (cHCC-CCA)

Hepatocellular carcinoma (HCC)

Cholangiocarcinoma (CCA)

Intrahepatic cholangiocarcinoma (iCCA)

Fibrolamellar carcinoma (FLC)

Hepatic hemangioendothelioma (HEE)

Hepatic angiosarcoma (HAS)

Intermediate cell carcinoma (INT)

Cholangiolocellular carcinoma (CLC)

Classical type (CT)

Typical subtype (TS)

Stem cell subtype (SC)

World Health Organization (WHO)

Hepatitis B(HBV)

Hepatitis C (HCV)

Alpha-fetoprotein (AFP)

Hepatocyte Specific Antigen Antibody (HepPar1)

Anti-Epithelial Cell Adhesion Molecule (EpCAM)

Human Glypican 3 (GPC3)

Spalt like transcription factor 4 (SALL4)

Cytokeratin 7 (CK7)

Cytokeratin 19 (CK19)

Carbohydrate antigen 19-9 (CA19-9)

American College of Radiology's liver imaging reporting and data system (LI-RADS)

Computed tomography (CT)

Magnetic resonance imaging (MRI)

Arterial phase hyper-enhancement (APHE)

CEUS (contrast-enhanced ultrasound)

Radio-embolization (SIRT)

Trans-arterial chemoembolization (TACE)

Liver resection (LT)
Liver transplantation (LT)
5-Fluorouracil (5-FU)
Overall survival (OS)
Fluorescence in situ hybridization (FISH)
Reverse transcription Polymerase chain reaction (Rt-PCR)
Whole exome sequencing (WES)
Whole genome sequencing (WGS)
Immunohistochemistry (IHC)
Epithelio-mesenchymal transition (EMT)
Erythroblast transformation-specific -related gene (ERG)

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Corresponding author:

Jean-Charles Nault MD, PhD
Service d'hépatologie, hôpital Jean Verdier
Avenue du 14 juillet, 93140 Bondy
TEL: +33 6 10 67 94 61
FAX: +33 1 53 72 51 92
Email: naultjc@gmail.com

Abstract

Hepatocholangiocarcinoma, fibrolamellar carcinoma, hepatic haemangioendothelioma and hepatic angiosarcoma represent less than 5% of primary liver cancers. If fibrolamellar carcinoma and hepatic haemangioendothelioma are driven by a unique somatic genetic alteration (*DNJBAB1-PRKCA* and *CAMTA1-WWTR1* fusion respectively), the pathogenesis of hepatocholangiocarcinoma remains more complex as suggested by its histological diversity. Histology is the gold standard for the diagnosis that remains often challenging even in an expert center due to the low incidences of these liver cancers. Resection, when feasible, is the cornerstone of the treatment together with liver transplantation for hepatic hemangioendothelioma. The role of loco-regional therapies and systemic treatments remains poorly studied. In this review, we aim to describe the recent advances in term of physiopathology and clinical care of these rare primary liver cancers.

Keywords: mixed tumor, hepatocholangiocarcinoma, fibrolamellar carcinoma, hepatic hemangioendothelioma, hepatocellular carcinoma, hepatic angiosarcoma

Hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCA) account, respectively, for 85% and 10% of all primary hepatic cancers (PLC). Large cohort studies and randomized controlled trials are available and have allowed to propose international guidelines for the management of HCC and CCA. In contrast, rare PLC such as combined hepato-cholangiocarcinoma (cHCC-CCA), fibrolamellar carcinoma (FLC), hepatic hemangioendothelioma (HEE) and hepatic angiosarcoma (HAS) lack of prospective studies and clinical trials due to their scarcity. Herein, we want to summarize the recent advances in physiopathology and management of rare PLC.

Combined tumors hepato-cholangiocarcinoma

A matter of definition

cHCC-CCA is characterized at histology by the presence of two distinct morphological patterns in the same lesion: HCC and intrahepatic CCA (iCCA)(1)(2).

Several classifications have been proposed (supplementary Table 1) and were used sequentially in the literature leading to confusion. The discussion about terminology, based on recent morphological and molecular advances, excluded several types of PLC from cHCC-CCA: collision tumors, hepatoblastoma, typical HCCs with immunohistochemical expression of progenitor markers; typical iCCAs with immunohistochemical expression of hepatocytic markers. Whether intermediate cell carcinoma (INT) and cholangiolocellular carcinoma (CLC) should be classified within cHCC-CCA was debated.

A recent proposal of a consensus terminology(3) divided PLC that cannot be included into either HCC or iCCA in three classes:

1. Tumors with the presence of hepatocytic and cholangiocytic histology mixed with a transition or separated areas within the same tumor, considered as combined HCC-CCA (cHCC-CCA).
2. PLC completely composed of “intermediate cells” (intermediate cell carcinoma), small cells of size intermediate between stem cells and hepatocytes with transitional morphology between hepatocytes and cholangiocytes, if this entity should be considered as a subtype of cHCC-CCA is still a matter of discussion(4,5).
3. PLC composed of pure CLC, if the main component of PLC is composed > 80% of cholangiolocarcinoma, finally reclassified in small duct iCCA(5).

According to this classification, the concept of “stem cell” phenotypes based on immunohistochemistry (EpCAM, CK19 and CD56) is not considered as a sub-category *per-se*, but rather as a feature that can be present in different types of PLC (4). Moreover, all subtypes of PLC could be associated in the same lesion with minor histological components observed in more than a half of cHCC-CCA(6,7). If different subtypes are present, a precise description is recommended and the percentage of each tumor type present should be assessed in surgical specimens(4).

Epidemiology and risk factors

Data from large databases reported a proportion of cHCC-CCA nearly 0.75% among all PLC with an incidence of 0.05/100 000 in the general population (8–10). The incidence in monocentric studies based on resection or necropsies varies from 2.4% to 5.3% of PLC and the 2018 World Health Organization (WHO) classification estimates the frequency at 2%-5%(1,4,5,11–15).

Risk factors associated with cHCC-CCA are shared with others PLC and include hepatitis B (HBV), hepatitis C (HCV), alcohol consumption, cirrhosis and male predominance (up to 79%) (Table 1). Association with cirrhosis is reported in several surgical series in eastern countries (26 to 81%); mostly associated with HBV infection(4,12,14,16–19). In Western countries, the rate of cirrhosis was up to 52% with HCV as the leading cause in Spain(43%) and USA(23%) and alcohol in France (40%)(13,20–22). These data are consistent with a systematic review identifying cirrhosis in 51.7% of liver explants or surgical pieces(18). It seems that cHCC-CCA stands at the crossroad between iCCA (low rate of cirrhosis and HBV/HCV infection) and HCC (high rate of cirrhosis and HBV/HCV infection) in term of underlying liver disease.

Genetic landscape of cHCC-CCA

Whole-genome sequencing of liver cancer displaying biliary phenotype including cHCC-CCA reports a median number of 60 to 70 non-synonymous coding mutations per tumor(Table 2)(23). *TERT* promoter, *TP53*, *ARID1A* and *ARID2* mutations are more frequent in cHCC-CCA, *PBRM1*, *BAP1*, *KRAS*, *IDH1* and *FGFR2* mutations in iCCA and *CTNNB1* mutations in HCC. The high heterogeneity in term of techniques and HCC-CCA classification of these studies needs to be underlined (24–27). Genomic analysis also suggest an impact of viral hepatitis (HCV and HBV) on the genetic landscape of cHCC-CCA that seems closer to HCC than iCCA in term of genomic profiles and prevalence of *TERT* promoter mutations(23).

The largest genetic study on cHCC-CCA was performed on 133 patients in Asia. *TP53*, *TERT* promoter, *AXIN1*, *KMT2D*, *ARID1A* were the leading mutations of cHCC-CCA, close to genomic alterations observed in HCC, even if the frequency of *TERT* promoter mutations (23%) seem lower than in HCC (40-60%) but higher than in iCCA (0-8%). The analysis of mutational signatures identified an exposure to aristolochic acid, aflatoxin B1 and hepatitis B. Epithelial mesenchymal transition, EpCAM, and KRT19 genes were mostly expressed in “combined” type cHCC-CCA with an enrichment of *KRAS* mutation. Xenobiotic and bile acid metabolism and overexpression of AFP, GPC3, and SALL4 were more represented in “mixed” type cHCC-CC according to the Allen Classification. The authors suggest that “mixed” type cHCC-CCA could be more similar to HCC and “combined” type cHCC-CCA more similar to iCCA(28).

Analysis of genetic landscape show that CLC has a different genetic profile compared to pure cHCC-CCA with more *ARID1A* and less *TERT* promoter mutation (29). Another genomic analysis confirms that CLC looks like a biliary-derived molecular entity harboring chromosomal stability, activation of TGF β pathway with biliary features(27).

In term of tumor heterogeneity, comparison of the iCCA and HCC component confirms the monoclonal origin of cHCC-CCA but also shows a significant intratumor genetic heterogeneity overlapping with the morphological heterogeneity(28,30). One study identified *TERT* promoter mutations in both HCC and iCCA components suggestive of an early event in carcinogenesis whereas mutations in other driver genes such as *TP53* harbored intratumoral heterogeneity(25).

In term of cell of origin, the disruption of p53 in mice promotes dedifferentiation of mature hepatocytes into nestin-positive progenitor cells that could give rise to HCC or iCCA under the influence of Wnt and Notch (31,32). Overexpression of nestin was identified in 81.3% of

human cHCC-CCA and was associated with a poor clinical outcome(28). Moreover, a cell line derived from cHCC-CCA can differentiate to both HCC and iCCA under different growth conditions (33,34). These results are consistent with the hypothesis that cHCC-CCA can derive from hepatic progenitor cells that express markers of both lineages (hepatocytes and biliary cells)(35,36).

These data suggest that 1) cHCC-CCA is monoclonal deriving from a common cell of origin 2) cHCC-CCA genomic features may be more similar to HCC than iCCA even if some cHCC-CCA harbored genomic features close to iCCA 3) risk factors can be associated specific genetic features in cHCC-CCA and 4) CLC has a different molecular profile close to iCCA.

Diagnosis

The diagnosis of cHCC-CCA is based on histology from biopsies or surgical specimens (Figure 2)(4,5). Immunohistochemical markers are not mandatory but could be helpful to better characterize PLC: hepatocyte markers (HepPar1, Alpha-fetoprotein and glypican-3); cholangiocytes markers (CK19, CK7) and “stem cells” markers (EpCAM, CK19, CD133)(4,22). These markers should be considered in the context of morphological analysis, especially for the “stem cells markers” that could be expressed by all PLC. In pre-surgical setting, the performance of liver biopsy for the diagnosis of cHCC-CCA could be estimated to 48% of sensitivity and 100% of specificity(22).

Sometimes the discordance between imaging and serum tumor markers (imaging suggestive of HCC with increased serum carbohydrate antigen 19-9 [CA19-9] or hypovascular nodule suggestive of iCCA with increased alpha-fetoprotein [AFP]) could rise the suspicion of a cHCC-CCA(12,17). However, serum biomarkers alone are not reliable for the diagnosis of cHCC-CCA with elevation of serum CA19-9 and AFP observed only in 45% of the cases with also a limited specificity(21)(37).

Even-though histology remains the gold standard for the diagnosis of cHCC-CCA, radiology (abdominal computed tomography (CT) or magnetic resonance imaging (MRI) with contrast agent injection) may help to suggest the diagnosis (Figure 2). Hallmarks of HCC (arterial phase hyper-enhancement [APHE] and washout) are observed in a minority of cHCC-CCA (21,22,38). Nevertheless, recent studies using the American College of Radiology’s liver imaging reporting and data system (LI-RADS) have reported misclassification of cHCC-CCA as HCC in 26% to 54% of cases when using major radiological features(39,40). Noticeably, 88% of these patients could be reclassified as malignant tumors but “non-HCC” (LI-RADS M category) after addition of ancillary features such as rim/peripheral arterial phase hyper-enhancement, progressive central enhancement, on portal venous and delayed phase images, predominantly peripheral washout appearance, liver surface retraction, biliary obstruction and marked diffusion restriction(39). The depiction of these features explain why the main differential diagnosis is often iCCA, and why performance of imaging is often insufficient(38,41–45). The association of HCC features with CCA features (appearance of iCCA with portal venous invasion, or appearance of HCC with biliary dilation or enlarged lymph nodes) may be suggestive of the diagnosis. Finally, CEUS (contrast-enhanced ultrasound) also harbors an insufficient specificity for the diagnosis of cHCC-CCA, since tumors show non-specific association of various degree of heterogeneous arterial phase hyperenhancement with washout (46,47).

Imaging has a limited diagnostic performance alone with a sensitivity of only 48% and a specificity of 81% and the combination of imaging and biopsy could improve the sensitivity (60%) and specificity (82%)(22). Overall, radiology is fundamental to guide liver biopsy (especially possible multiple biopsies in heterogeneous tumors) and to perform tumor staging.

Treatments

Liver resection

Liver resection (LR) is currently the most effective curative-intent therapy for cHCC-CCA. According to state-of-the-art principle for oncologic liver surgery, liver resection aims to completely remove the lesion with adequate margins and with a sufficient liver remnant volume. This requires a multi-parametric evaluation of the patient, tumor and underlying liver disease(48). A resection margin >10 mm has been associated with a prolonged disease-free survival(49). Major hepatectomy can be proposed if a sufficient liver remnant volume has been secured in order to limit the risk of postoperative liver failure(48). In patients with cirrhosis, evaluation of the degree of portal hypertension should also be performed as clinically significant portal hypertension represent absolute contraindications to major hepatectomy(50). Furthermore, lymphatic pattern of tumor spread in cHCC-CCA requires a routine hilar lymphadenectomy(51). The need for routine lymphadenectomy should currently restrict the use of the laparoscopic approach only to centers with extensive expertise both in liver surgery and laparoscopy (52).

A systematic review including 437 cHCC-CCA treated by LR reported a disease-free survival of 14.2 months in cHCC-CCA compared to 43.1 months in HCC and 17.8 months in iCCA with an overall survival of 37, 67 and 32 months respectively(18). Outcomes after liver resection for cHCC-CCA seems close to patients with iCCA and worse than patients with HCC mainly due to early tumor recurrence (13,17) even if a recent study identify no difference of outcomes after adjustment on cirrhosis and tumor size(53).

Liver transplantation

The role of liver transplantation (LT) for the treatment of small iCCA or cHCC-CCA remains controversial. A systematic review of retrospective studies for LT for cHCC-CCA reported a median disease-free survival of 14.2 months and a median OS of 37.1 months(18). These results were discouraging and, in many countries, cHCC-CCA is still a contraindication for LT.

In contrast, recent studies with similar inclusion criteria reported more positive outcomes. The first study conducted in Spain on 42 patients undergoing LT for HCC with an incidental diagnosis of HCC-CC or iCCA and stratified according to tumor size and number. The 5-years survival rates were similar between cHCC-CCA and HCC controls (78% vs 86%). Patients with multinodular or uninodular tumors larger than 2 cm had the worst outcomes(20). The second retrospective study analyzed patients treated by resection (n=26) or LT (n=95) for iCCA and cHCC-CCA <5cm developed on cirrhosis. Overall survival (67% at 5 years) and recurrence-free survival (75% at 5 years) were better in patients treated by LT than in patients treated by resection and small tumor. iCCA and cHCC-CCA patients had comparable survival(54).

Recent retrospective data suggest that cirrhotic patients with cHCC-CCA transplanted have a better survival than patients resected if tumor size is <5 cm(20,54,55). One of the main drawbacks of these studies is that cHCC-CCA was identified incidentally on the explant and data on intention-to-treat analysis of LT for cHCC-CCA diagnosed before inscription on the waiting list are lacking. A recent consensus concluded that there is not enough evidence to propose LT for cHCC-CCA but that this approach should be explored in clinical trials(56). Moreover, liver transplantation should be also discussed according to each national guidelines.

Loco-regional treatments

The effectiveness of trans-arterial chemoembolization (TACE) on cHCC-CCA was analyzed in retrospective studies including a limited number of patients. TACE in 50 patients induced a partial response or stable disease in 70% of the cases, mainly in tumors with APHE with a median overall survival of 12.3 months(57).

Better outcomes were reported in a cohort of patients treated by TACE for recurrence after liver resection. As expected, cHCC-CCA with a non-rim APHE pattern at imaging have a better radiological response rate (36% vs 0%) and survival (52.8 vs 12.4 months) compared to patients with rim APHE (58,59). Data about radio-embolization (SIRT) and chemotherapy on unresectable iCCA show that 22% of patients can be downstaged to surgical intervention(60). SIRT are associated with a 55% radiological response rate, 65% disease control rate with a median overall survival of 9.3 months in 21 patients suggesting a possible role of SIRT for cHCC-CCA (61).

Altogether, only few data are currently available to support the value of intra-arterial treatments in patients with cHCC-CCA, even if some retrospective data suggest a possible role in selected patients with tumor showing APHE.

Systemic treatments

Data about systemic treatments in unresectable cHCC-CCA are limited to few retrospective series testing the first-line treatment approved for advanced HCC (sorafenib) and CCA (gemcitabine/platinum regimens)(62,63).

A multicentric Japanese study on 36 patients with unresectable cHCC-CCA analyzed different first-line systemic treatments. The median overall survival of the gemcitabine/cisplatin, fluorouracil/cisplatin and sorafenib was 11.9, 10.2 and 3.5 months respectively suggesting that sorafenib was associated with a reduced survival(64). A French multicentric study included 30 patients treated by gemcitabine with oxaliplatin or cisplatin +/- bevacizumab. 8 patients (28.6%) had a partial response with a median progression free survival of 9.0 months and an overall survival of 16.2 months.(65). The largest series available is a monocentric cohort of 68 unresectable cHCC-CCA who received mainly gemcitabine-based regimen (57/68) with 23.5% gemcitabine +/- fluoropyrimidine and 60.3% gemcitabine with platinum. Overall survival was 11.5 months in patients receiving gemcitabine/platinum therapy and 9.6 months in the 7 patients treated with sorafenib alone(66). Currently, no data in literature are available regarding the use of atezolizumab/bevacizumab, lenvatinib, cabozantinib and ramucirumab in cHCC-CCA.

To summarize, systemic treatment based on gemcitabine/platinum regimens is the most widely used drug but is not supported by a high level of evidence. The role of sorafenib remains unknown.

Fibrolamellar carcinoma

FLC is a rare primary liver cancer derived from hepatocytes occurring in young adults (sex ratio 1/1) in normal liver (Figure 3)(67–72). It is characterized by eosinophilic polygonal cells and prominent nucleoli with fibrotic tissue surrounding tumor cells at histology(67,72,73). No risk factors of FLC development have been identified so far. Most of FLC are diagnosed before 40 years with a median age of diagnosis ranged from 20-29 years(76–78). FLC are bigger in size (9-13 cm) with a higher rate of invasion of lymph node (43-46%) invasion compared to HCC(70,74–76). The most frequent localization of metastasis are lung (50%), bone (19.2%), and brain (1.9%)(77).

Physiopathology

At the molecular level, *DNJBAB1-PRKCA* fusion due to a focal deletion in the chromosome 19 is identified in almost all FLC and is considered as highly specific but not pathognomonic (Table 2)(78–80). The same fusion was identified in a some intraductal oncocytic papillary neoplasms of the pancreas and bile duct(81,82)(82)(82)(82). A subset of HCC with fibrolamellar-like features occurred in non-cirrhotic liver but in older patients and was characterized by both *BAP1* alterations and an aberrant activation of protein kinase A pathway due to a chromosome gain of *PRKACA* combined with a loss of *PRKAR2A* (the inhibitory regulatory subunit of PKA)(83). These tumors also expressed neuroendocrine and pancreatic markers underlining a potential origin from hepato-pancreatic progenitor. Finally, *GNAS* mutations leading to protein kinase A activation were observed in a subset of hepatocellular adenomas with a fibrous stroma(84). All these data suggested that protein kinase A activation in the liver was associated with “fibrolamellar-like” features and underlined a link between the activation of protein kinase A and a hepato-pancreatic progenitor lineage. Finally, rare cases of FLC arising in patients with Carney complex were related to *PRKAR1A* germline inactivating mutations(Table 2)(85). *PRKCA* from the fusion *DNJBAB1-PRKCA* has a conserved tyrosine kinase domain and an enhanced cAMP-stimulated protein kinase A activity. It leads to a constitutive activation of PKA pathway and promote malignant transformation of hepatocytes in mouse model(86,87)(87)(87)(87). As *DNJBAB1-PRKCA* fusion is a genetic footprint of FLC, it could be used to confirm the diagnosis of FLC using FISH or RT-PCR in clinical practice(80,88)(88)(88)(88).

Diagnosis

Most of the time diagnosis is made in a symptomatic patient with abdominal pain and weight loss(73). Rarely, obstructive jaundice, gynecomastia in males, encephalopathy, ascites, acute liver failure, recurrent thrombophlebitis, anemia, hypoglycemia or Budd-Chiari syndrome can reveal FLC(89–91). Differential diagnosis consists of primary liver tumor with fibrosis such as some subtype of HCC (especially *BAP1* mutated HCC), CCA or focal nodular hyperplasia.

The diagnosis of FLC could be suspected on CT and MRI taking into account the clinical context (young patient without chronic liver disease). FLC are usually large and lobulated heterogeneous lesions with a central stellate scar seen in 65–70% of the cases and with tumor

calcifications and abdominal lymphadenopathy observed in half of the cases (92,93). On MRI, FLC show T1-weighted hypointensity and T2-weighted hyperintensity with a central area showing hypointense on both T1- and T2-weighted images (92). FLC show heterogeneous hyperenhancement on arterial phase with a variable enhancement pattern on portal venous and delayed phases at CT scan and MRI(90). Noticeably, FLC never contain fat, and do not invade hepatic or portal veins in contrast to classical HCC. FLC are also hypointense on the hepatobiliary phase using hepatobiliary contrast agents(94). FLC don't usually produce detectable AFP and less than 10% of patients show increased AFP level above 200ng/mL(89). Tumor and non-tumor liver biopsy is advised in most of the cases in clinical practice with the exception of patients eligible to surgery in front line whatever the results of the biopsy(91,95). High rate of for CK7 and CD68 positive staining on liver samples and low rate of glypican-3 positive staining could differentiate FLC from regular HCC(96,97).

Treatment

In a systematic review including 575 patients, those treated with partial hepatectomy (55%) had 5-year overall survival reaching 70%(76). Liver resection was associated with a better overall survival (OS) in patients with FLC compared to patients with classical HCC (median OS of 84.9 vs. 42.9 months, respectively). However, no significant difference in 5-year survival could be observed when focusing on FLC and HCC patients without cirrhosis, suggesting that the difference observed in the overall population was likely related to the severity of the underlying liver disease (69,71,77). Currently, liver resection remains the most effective curative-intent treatment option for FLC, aggressive initial surgical resection along with regional lymphadenectomy being advised (75,76).

In contrast, results of LT are impaired by a high rate of tumor recurrence leading to a 5-year overall survival of 35%(76). However, the absence of selection criteria for patients treated by liver transplantation limits the conclusion drawn from these studies(71,76,98). Slightly better results were recently reported on 63 patients with an overall survival of 48% at 5 years(99). As other indications, liver transplantation should be also discussed according to national guidelines.

Patient with unresectable disease (20 to 25% at diagnosis) are treated with various combinations of systemic therapy, with or without locoregional therapies. The role of TACE or SIRT alone is also poorly studied in the literature. Chemotherapy regimens were 5-Fluorouracil (5-FU) +cisplatin or irinotecan, doxorubicin and gemcitabin+oxaliplatin but few patients exhibited radiological response(100). Sorafenib was associated with stable disease in 4 out of 9 patients and one patient harbored a complete response with anti-PD1 antibody(101). Moreover, aurora kinase A inhibitors showed a limited anti-tumor effect in a phase 2 clinical trial(102). Shutdown of PRKCA pathway and targeting the *DNABJ1-PRKACA* fusion is an appealing therapeutic avenue. If several therapeutic targets have been proposed in FLC such as inhibitor of the kinase pocket of the fusion protein or the combination of Hsp70 and MEK inhibitor(103)(104), currently no efficient targeted therapy has been validated.

Hepatic epithelioid Haemangioendothelioma

HEE is a rare vascular tumor developed on normal liver, characterized by epithelioid and histiocytoid vascular endothelial cells in a fibrotic stroma (Figure 4)(105). Tumor cells are positive for endothelial marker (facteur VIII related antigen, CD34 and CD31) at

immunohistochemistry(105). Tumors cells likely invade pre-existing vascular channels including centrilobular veins at the periphery. Some risk factors have been suggested in the literature such as oral contraception, vinyl chloride, thorotrast, asbestos, or viral hepatitis even if the level of evidence is low(106,107).

Hemangioendothelioma was described in 1982 as a vascular neoplasia affecting different organs with a prevalence of less than one per million(108–110). The most common organ involved are liver alone (21%), liver and lung (18%), lung alone (12%) and bone alone (14%) but any site in the body can be affected(106,111). HEE is more frequent in female (61% to 80%)(106,109). The clinical behaviour is heterogeneous from indolent to aggressive behavior(111).

Advances in knowledge of the physiopathology

Recurrent *CAMTA1-WWTR1* fusion due to a translocation t(1;3)(p36.3;q25) with *CAMTA1* as a calmodulin-binding transcription activator and *WWTR1* (coding for TAZ) as a transcriptional coactivator is pathognomonic of HEE(Table 2)(112). In cellulo, *CAMTA1-WWTR1* fusion results in nuclear localization of the fusion protein and lead to a constitutive activation of the hippo pathway through a TAZ-dependent transcriptomic program(113). Around 90% of HEE harbor the *CAMTA1-WWTR1* fusion and this fusion was identified whatever the primary site of hemangioendothelioma (114). Moreover, rare *YAP1-TFE3* fusion has been identified in HEE without *CAMTA1-WWTR1* fusion(Table 2)(115,116). Detection of *CAMTA1-WWTR1* fusion by FISH or RT-PCR or nuclear *CAMTA1* expression at immunohistochemistry is useful to confirm the diagnosis of HEE as there have not been identified in other human tumors(116,117).

Diagnosis

A systemic review including 402 patients with HEE reported that 25% were asymptomatic whereas right upper quadrant pain (48.6%), hepatomegaly (20.4%) and weight loss (15.6%) were the most frequent symptom at diagnosis. Extrahepatic metastasis were observed in 36.6% of patients(107). HEE could be nodular or diffuse and nodular lesions are usually multiple and affect both lobes of the liver.

A HEE should be suspected in front of multifocal nodules (88%), sometimes coalescent, or presence of nodules in subcapsular regions (up to 96%) with a capsular retraction (50 to 80%) at imaging(118–120). Presence of a ring enhancement at the tumor periphery on arterial phase is observed in 33% of patients with a target appearance on the portal venous phase in 69% of cases explained by a central fibrosis with a concentric layer of tumor cells and a peripheral avascular rim at histology. On MRI, HEE harbored a target appearance on the T2-weighted sequences in 67% and on the diffusion-weighted sequences in 61% patients(120). Histology is the gold standard for the diagnosis of HEE with the help of immunohistochemistry (endothelial markers factor VIII related antigen, CD34 and CD31). The differential diagnosis with hepatic angiosarcoma is sometimes difficult to perform at histology and identification of *CAMTA1-WWTR1* fusion could be useful to confirm the diagnosis of HEE(121).

Treatment

Therapeutic option in HEE should take into account tumor burden, extrahepatic metastasis, resectability, age and comorbidities. The pattern of progression (stability versus slow or rapid progression) should be also assessed before therapeutic decision.

A comprehensive review of the literature reported the use of LT in 44.8% of patients, followed by no treatment in 24.8%, chemotherapy or radiotherapy in 21% and liver resection in 9.4% (107). The results of LT for HEE were reported in multicentric database of 131 patients with a 5-year overall survival of 77.2%(122). Moreover, patients with extrahepatic metastasis could achieve prolonged survival after LT (up to 78% at 10 years)(123).

Risk factors for recurrence after LT were macrovascular invasion, waiting time of less than 3 months and LN metastasis(124). Retrospective study has suggested that resection or LT in HEE could achieved the same outcomes with the limit of inclusion of more advanced stages in patients treated by LT(125). As HEE is often a bilobar disease rarely amenable to liver resection, LT might be the best option even for patients with extrahepatic metastasis (126).

In non-resectable or non-transplantable patients, different systemic treatments such as interferon alpha, thalidomide, doxorubicin, intra-arterial 5-fluorouracil, bevacizumab has been used in a very limited number of cases(121). Sorafenib used in a pilot study of 15 patients affected by HEE of different localization, the median progression-free survival was 6 months (127). In a subset of patients with indolent disease, careful follow-up can be an option, recent data reporting a 10-years OS of 41% in selected patients (128,129). As no systemic treatment is currently approved for the treatment of HEE, a better understanding of the biological consequences of *CAMT1-WWTR1* fusion can be helpful in order to identify new targeted therapy.

Hepatic angiosarcoma

HAS is a high-grade aggressive mesenchymal malignancy defining a subtype of soft-tissue sarcoma composed of malignant endothelial tumoral cell of vascular or lymphatic origin developed mostly on normal liver (Figure 5). HAS is exceptional with an incidence estimated at 0.5-2.5 cases for 10,000,000 persons developed mostly in males(ratio 3:1)(130–132). In the sixties, 25% of HAS were associated to environmental risk factors such as vinyl chloride monomer, thorotrast, anabolic steroids and arsenic(133). HAS associated due to vinyl chloride monomer could be developed on cirrhosis (up to 20 to 43%)(134–136). With the control of exposure to vinyl chloride in workers in the 70s, the incidence of HAS declined(137,138).

Physiopathology

Overall, few data on molecular analysis is currently available. *KRAS* mutations have been described in sporadic cases as well as *TP53* mutations in vinyl chloride related HAS and recently a *ROS1-GOPC/FIG* fusion has been identified in one HAS(139–141).

Diagnosis

Most of the time, patients with HAS have symptoms at presentation such as abdominal pain, fatigue, weight loss, hepatosplenomegaly, ascites, jaundice, and anemia. The intraperitoneal rupture of HAS was reported in 15–27% of patients(142). HAS has a very aggressive behavior and poor prognostic factors are older age, large tumor size and high Ki-67 index(130,132). 219 patients analyzed in a recent systematic review have an average age of 56.7 years and 31.5% of distant metastasis. The median overall survival time was 6 months, with a 2-year survival of 17.3%(143).

At contrast-enhanced imaging, HAS is usually multifocal and with heterogeneous patterns such as a progressive enhancement without washout at the portal and delayed phase. Progressive centripetal or diffuse “flash-fill” enhancement pattern (“reverse haemangioma”) with centrifugal enhancement have also been reported(135,144). HAS often contain hemorrhagic area resulting in heterogeneous lesions on MRI with hyperintense zones on T1WI and hypointense on T2WI(144).

Some controversy exists about the performance of liver biopsy and about a potential high risk of bleeding (136,142,145). However, histology remains the gold standard for the diagnosis of HAS and liver biopsy is required to confirm the diagnosis(132). HAS is heterogeneous at histology ranging from well-defined anastomotic vessels (vasoformative) to solid sheets of epithelioid or spindle cells without vasoformation with different patterns sometimes mixed in the same tumors(130). HAS expresses ERG and endothelial markers as CD31 and CD34 at immunohistochemistry(146).

Treatment

Surgical resection seems the best therapeutic option offering a median survival between 17 and 19 months(142,147). All the studies about LT confirmed the limited survival (around 6 months) with most of patients dying from tumor recurrence explaining why HAS is a contraindication to LT (148,149). It is important to note that only 30% of patients had a known pre LT diagnosis of HAS(125).

Transarterial embolization is frequently used to treat tumor bleeding with a limited impact on survival(143). There is no approved chemotherapy regimen for non-resectable liver HAS. ESMO guidelines on Sarcomas reports that angiosarcomas in general are sensitive to taxanes, reporting gemcitabine as an alternative alone or in combination with docetaxel(150).

In a phase II trial including three primary liver angiosarcomas in patients with metastatic or unresectable disease weekly paclitaxel achieved a progression-free survival rates of 74% and 45% at 2 and 4 months respectively, with a median overall survival of 8 months(151). Palliative chemotherapy such as 5-FU with doxorubicin or ifosfamide, carboplatin, bevacizumab or sorafenib have been reported mostly in case reports or small series with limited radiological response and poor survival(132). Due to the rarity of this cancer the management of HAS should be made in centers with multidisciplinary expertise on sarcomas.

Conclusion

Despite several advances in the last decades mainly in the field of physiopathology, rare PLC suffer from their condition of orphan diseases with pitfalls in term of diagnosis and limited availability of dedicated prospective collection of clinical data and limited cases to clinical trials. Moreover, grants dedicated to these PLC are lacking and pharmaceutical companies are rarely interested in the development of new drugs for these patients. In order to bypass these limitations, large international consortiums are needed in the future to rise grant to run large prospective cohort and better define rare PLC in term of physiopathology and clinical behavior. This cooperative network will be also the basis of future clinical trials.

KEY POINTS:

- 1) Recent consensus has reclassified pure cholangiolocarcinoma in CCA whereas cHCC-CCA are characterized histologically by the presence of two distinct morphological patterns in the same lesion
- 2) A unique genetic alteration drives the pathogenesis of fibrolamellar carcinoma (*DNJBAB1-PRKCA* fusion) and hepatic haemangioendothelioma (*CAMTA1-WWTR1* fusion)
- 3) Combination of evocative imaging followed by histological evidence, mainly using tumor and non-tumor biopsy, are required for the diagnosis of rare PLC
- 4) Liver resection is the main treatment of rare PLC when feasible
- 5) No systemic or locoregional therapies are currently validated in the treatment of any of unresectable PLC
- 6) Liver transplantation is validated for hepatic hemangioendothelioma even in a metastatic setting whereas is still an area of research for small cHCC-CCA

Table 1: recent data on risk factors of hepatocholangiocarcinoma

| Author | Country | Numbers of patients | Advanced fibrosis | HCV | HBV | Alcohol | Metabolic Syndrome |
|-------------------------|-------------------|---------------------|-------------------|-------------|---------------|--------------|--------------------|
| Sasaki et al. 2017(26) | Japan | 53 | 14/24 (58%) | 9/19 (47%) | 9/44 (21%) | 2/19 (11%) | 3/19 (16%) |
| Zhou et al 2017(152) | China | 144 | 91/144 (63.2%) | - | 101/144 (70%) | 29/144 (20%) | - |
| Xue et al. 2019(28) | China | 121 | 54/115 (47%) | 2/115 (2%) | 89/115 (77%) | - | - |
| Okumura et al 2020(153) | Japan | 89 | 30/89 (34%) | 29/89 (33%) | 37/89 (43%) | - | - |
| Gentile et al 2019(18) | Systematic Review | 437 | 226/437 (52%) | 39/437 (9%) | 264/437 (60%) | - | - |
| Wells et al 2015(21) | USA | 39 | 12/39 (31%) | 9/39 (23%) | 0/39 | 3/39 (8%) | 2/39 (5%) |
| Gigante et al 2019(22) | France | 20 | 10/20 (50%) | 1/20 (4%) | 3/20 (15%) | 8/20 (40%) | 6/20 (30%) |
| De Martin 2020*(54) | France | 31 | 31/31 (100%)* | - | - | 40/75 53% | - |
| Holzner 2020(53) | USA | 47 | 20/47 (43%) | 15/47 (32%) | 22/47 (47%) | - | - |

We included recent studies with histologically confirmed (Goodman transitional type (type II)/Allen and Lisa type B or C/WHO classical type tumors and stem cell type with exception of CLC, studies already included in the systematic review (Gentile et al. 2019) are not shown.

*Study including only lesions on cirrhosis. Data about risk factor prevalence are relatives to the entire cohort of cHCC-CCA and iCCA

Table 2: genomic alterations in rare primary liver cancers

| Study | Classification | Type of analysis | N patients Subtypes | Fibrosis (F3-F4) | Somatic genetic alterations |
|---------------------------------|--------------------|-----------------------------------|---------------------------------------------------------------|------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Hepatocellular carcinoma | | | | | |
| Cazals-Hatem 2004(154) | Lisa et Allen 1949 | Target sanger sequencing | 14 mixed, 1 fibrolamellar HCC 3 collision tumors | 3/15 | <i>TP53</i> |
| Fujimoto 2015(23) | WHO 2010 | WGS and RNA-seq | 30 Liver cancer with biliary phenotype 7cHCC-CCA +2CLC | 4/9 | <i>TERT</i> promoter 53%, <i>PBMR1</i> 20%, <i>ARID2</i> 27% |
| Sasaki 2017(26) | WHO 2010 | Target sanger sequencing + IHC | 53 mixed tumors 4 CT, 4 TS, 20 INT, 25 CLC | 38/53 | cHCC-CCA: <i>TERT</i> 50%, <i>TP53</i> 25%, <i>KRAS</i> 50% <i>ARID1A</i> 0% Intermediate: <i>TERT</i> 42%, <i>TP53</i> 58%, <i>KRAS</i> 5%, <i>ARID1A</i> 11% |
| Moeini 2017(27) | WHO 2010 | Microarray, DNA copy number, WES | 18 mixed tumors 6 CLC / 8SC / 4CT | 10/18 | CLC: <i>TP53</i> and <i>IDH1</i> cHCC-CCA: <i>TP53</i> , <i>TERT</i> promoter, <i>BRAF</i> , <i>FGFR2-BICC1</i> fusion |
| Liu 2018(24) | WHO 2010 | WGS, WES and RNA-seq | 4 cHCC-CCA not specified | NA | <i>TP53</i> , <i>CTNNB1</i> and <i>ARID1A</i> |
| Wang 2018(30) | WHO 2010 | WES | 7 cHCC-CCA | NA | <i>TP53</i> and <i>ARID2</i> |
| Xue 2019(28) | Lisa et Allen 1949 | WES, WGS, RNA-seq | 121 tumors: 6 separate type, 56 combined type, 59 mixed type. | 54/115 | <i>TP53</i> 49%, <i>TERT</i> promoter 23%, <i>AXIN</i> 10%, <i>KMT2D</i> 9%, <i>KEAP1</i> 8%, <i>ARID1A</i> 8%, <i>RB1</i> 8%, <i>CTNNB1</i> 6%, <i>IDH1</i> 5% |
| Joseph 2019(25) | Consensus 2019 | Target next-generation sequencing | 20CT | 15/18 | <i>TP53</i> (80%), <i>TERT</i> (70%), <i>ARID1A</i> (15%), <i>CTNNB1</i> (10%), <i>AXIN1</i> (10%), <i>KRAS</i> (5%) |
| Sasaki 2019(29) | Consensus 2019 | Target sequencing + IHC | 9 CT | 6/9 | <i>TP53</i> (66%), <i>TERT</i> promoter (33%), <i>KRAS</i> (22%) |
| Fibrolamellar carcinoma | | | | | |
| Honeyman 2014 (78) | NA | RNA seq | 15 FLC | 0 | <i>DNAJB1-PRKACA</i> fusion (100%) |
| Cornella 2015(79) | NA | FISH WES | 78 FLC | 0 | <i>DNAJB1-PRKACA</i> fusion (79%) <i>BRCA2</i> (4.2%) |
| Graham 2015(80) | NA | RT-PCR FISH | 26 FLC | 0 | <i>DNAJB1-PRKACA</i> fusion (100%) |
| Graham 2018(85) | NA | FISH NGS | 3 FLC without <i>DNAJB1-PRKACA</i> fusion | 0 | <i>PRKAR1A</i> (100%) in patients with Carney syndrome and FLC |
| Graham 2018(155) | NA | FISH | 104 typical FLC, 12 probable FLC and 9 unlikely FLC | 0 | 99% <i>DNAJB1-PRKACA</i> fusion in typical, 75% in probable and 0% in unlikely FLC |
| Hepatic haemangioma | | | | | |
| Tanas 2011 (112) | NA | RNA seq FISH | 47 haemangioma (hepatic and non-hepatic) | 0 | 89% <i>WWTR1-CAMTA1</i> fusion |
| Errani 2011(114) | NA | FISH | 17 haemangioma (hepatic and non-hepatic) | 0 | 100% <i>WWTR1-CAMTA1</i> fusion |
| Antonescu 2013(115) | NA | FISH | 10 haemangioma without <i>WWTR1-CAMTA1</i> | 0 | 100% <i>YAP1-TFE3</i> fusion (in tumors without <i>WWTR1-CAMTA1</i> fusion) |
| Flucke 2014(156) | NA | FISH RT-PCR | 35 haemangioma (hepatic and non-hepatic) | 0 | 94% <i>WWTR1-CAMTA1</i> and 6% <i>YAP1-TFE3</i> fusion |
| Patel 2015(116) | NA | RT-PCR | 18 haemangioma (hepatic and non-hepatic) | 0 | 78% <i>WWTR1-CAMTA1</i> and 6% <i>YAP1-TFE3</i> fusion |

Molecular alterations of HAS were not represented as very few data are currently available in the literature CLC = cholangiocarcinoma, WES = whole exome sequencing, WGS = whole genome sequencing, IHC = immunohistochemistry, CT = classical type, TS = typical subtype, INT = intermediate subtype, CLC = cholangiocellular subtype, SC= stem cell subtype, EMT= epithelio-mesenchymal transition

Figure 1: main characteristics of hepatocholangiocarcinoma

We figured the main genetic alterations, clinical, histological and pathological and radiological features as well the treatment available of cHCC-CCA

Figure 2: histological and radiological features of hepatocholangiocarcinoma

In the upper panel we represented classical cHCC-CCA (upper panel, left) with the HCC (positive for Glypican 3) and CCA (positive for CK7) components as well as intermediate cell carcinoma (positive for CD133) (upper panel, right)

In the middle panel we represented HCC with stem cell features (middle panel, left) at immunohistochemistry (positive for Glypican 3 and for CK19) and cholangiocarcinoma recently reclassified as iCCA (middle panel right).

In the lower panel, we figured an example of a MRI of cHCC-CCA with a well-delineated heterogeneous lesion with capsular retraction. The lesion harbored progressive delayed enhancing areas mixed with areas with arterial enhancement and washout.

Figure 3: main characteristics of fibrolamellar carcinoma

We figured the main genetic alterations, clinical, histological and pathological and radiological features as well the treatment available of FLC

Figure 4: main characteristics of hepatic haemangioendothelioma

We figured the main genetic alterations, clinical, histological and pathological and radiological features as well the treatment available of HEE

Figure 5: main characteristics of hepatic angiosarcoma

We figured the main genetic alterations, clinical, histological and pathological and radiological features as well the treatment available of HAS

References

1. Allen RA, Lisa JR. Combined Liver Cell and Bile Duct Carcinoma. *The American Journal of Pathology*. 1949;25:647–655.
2. Koster H, Kasman LP. Primary duplex liver carcinoma. *The American Journal of Surgery*. 1932;17:237–241.
3. Nagtegaal ID, Odze RD, Klimstra D, Paradis V, Rugge M, Schirmacher P, et al. The 2019 WHO classification of tumours of the digestive system. *Histopathology* [Internet]. 2019 [cited 2019 Sep 16];0. Available from: <https://doi.org/10.1111/his.13975>
4. Brunt E, Aishima S, Clavien P-A, Fowler K, Goodman Z, Gores G, et al. cHCC-CCA: Consensus terminology for primary liver carcinomas with both hepatocytic and cholangiocytic differentiation. *Hepatology*. 2018;68:113–126.
5. Sempoux C, Kakar S, Kondo F, Schirmacher P. Combined hepatocellular-cholangiocarcinoma and undifferentiated primary liver carcinoma. In: *WHO Classification of Tumours: Digestive System Tumours, 5th*, Arends MJ, Fukuyama M, Klimstra DS, et al (Eds), IARC, Lyon 2019. p.260.
6. Sasaki M, Sato H, Kakuda Y, Sato Y, Choi JH, Nakanuma Y. Clinicopathological significance of ‘subtypes with stem-cell feature’ in combined hepatocellular-cholangiocarcinoma. *Liver Int*. 2015;35:1024–1035.
7. Akiba J, Nakashima O, Hattori S, Tanikawa K, Takenaka M, Nakayama M, et al. Clinicopathologic analysis of combined hepatocellular-cholangiocarcinoma according to the latest WHO classification. *The American journal of surgical pathology*. 2013;37:496–505.
8. Garancini M, Goffredo P, Pagni F, Romano F, Roman S, Sosa JA, et al. Combined hepatocellular-cholangiocarcinoma: a population-level analysis of an uncommon primary liver tumor. *Liver Transpl*. 2014;20:952–959.
9. 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.
10. Kudo M, Izumi N, Kubo S, Kokudo N, Sakamoto M, Shiina S, et al. Report of the 20th Nationwide follow-up survey of primary liver cancer in Japan. *Hepatol. Res*. 2020;50:15–46.
11. Goodman ZD, Ishak KG, Langloss JM, Sesterhenn IA, Rabin L. Combined hepatocellular-cholangiocarcinoma. A histologic and immunohistochemical study. *Cancer*. 1985;55:124–135.
12. Ng IO, Shek TW, Nicholls J, Ma LT. Combined hepatocellular-cholangiocarcinoma: a clinicopathological study. *J. Gastroenterol. Hepatol*. 1998;13:34–40.

13. Jarnagin WR, Weber S, Tickoo SK, Koea JB, Obiekwe S, Fong Y, et al. Combined hepatocellular and cholangiocarcinoma: demographic, clinical, and prognostic factors. *Cancer*. 2002;94:2040–2046.
14. Lee W-S, Lee K-W, Heo J-S, Kim S-J, Choi S-H, Kim Y-I, et al. Comparison of combined hepatocellular and cholangiocarcinoma with hepatocellular carcinoma and intrahepatic cholangiocarcinoma. *Surg. Today*. 2006;36:892–897.
15. Edmondson HA, Steiner PE. Primary carcinoma of the liver: a study of 100 cases among 48,900 necropsies. *Cancer*. 1954;7:462–503.
16. Taguchi J, Nakashima O, Tanaka M, Hisaka T, Takazawa T, Kojiro M. A clinicopathological study on combined hepatocellular and cholangiocarcinoma. *J. Gastroenterol. Hepatol*. 1996;11:758–764.
17. Liu C-L, Fan S-T, Lo C-M, Ng IO-L, Lam C-M, Poon RT-P, et al. Hepatic resection for combined hepatocellular and cholangiocarcinoma. *Arch Surg*. 2003;138:86–90.
18. Gentile D, Donadon M, Lleo A, Aghemo A, Roncalli M, di Tommaso L, et al. Surgical Treatment of Hepatocholangiocarcinoma: A Systematic Review. *Liver Cancer*. 2020;9:15–27.
19. Zhou Y-M, Zhang X-F, Wu L-P, Sui C-J, Yang J-M. Risk factors for combined hepatocellular-cholangiocarcinoma: A hospital-based case-control study. *World J Gastroenterol*. 2014;20:12615–12620.
20. Sapisochin G, de Lope CR, Gastaca M, de Urbina JO, López-Andujar R, Palacios F, et al. Intrahepatic Cholangiocarcinoma or Mixed Hepatocellular-Cholangiocarcinoma in Patients Undergoing Liver Transplantation: A Spanish Matched Cohort Multicenter Study. *Annals of Surgery [Internet]*. 2014;259. Available from: https://journals.lww.com/annalsofsurgery/Fulltext/2014/05000/Intrahepatic_Cholangiocarcinoma_or_Mixed.17.aspx
21. Wells ML, Venkatesh SK, Chandan VS, Fidler JL, Fletcher JG, Johnson GB, et al. Biphenotypic hepatic tumors: imaging findings and review of literature. *Abdominal Imaging*. 2015;40:2293–2305.
22. Gigante E, Ronot M, Bertin C, Ciolina M, Bouattour M, Dondero F, et al. Combining imaging and tumour biopsy improves the diagnosis of combined hepatocellular-cholangiocarcinoma. *Liver Int*. 2019;39:2386–2396.
23. Fujimoto A, Furuta M, Shiraishi Y, Gotoh K, Kawakami Y, Arihiro K, et al. Whole-genome mutational landscape of liver cancers displaying biliary phenotype reveals hepatitis impact and molecular diversity. *Nature communications*. 2015;6:6120.
24. Liu Z-H, Lian B-F, Dong Q-Z, Sun H, Wei J-W, Sheng Y-Y, et al. Whole-exome mutational and transcriptional landscapes of combined hepatocellular cholangiocarcinoma and intrahepatic cholangiocarcinoma reveal molecular diversity. *Biochim Biophys Acta Mol Basis Dis*. 2018;1864:2360–2368.

25. Joseph NM, Tsokos CG, Umetsu SE, Shain AH, Kelley RK, Onodera C, et al. Genomic profiling of combined hepatocellular-cholangiocarcinoma reveals similar genetics to hepatocellular carcinoma. *J. Pathol.* 2019;248:164–178.
26. Sasaki M, Sato Y, Nakanuma Y. Mutational landscape of combined hepatocellular carcinoma and cholangiocarcinoma, and its clinicopathological significance. *Histopathology.* 2017;70:423–434.
27. Moeini A, Sia D, Zhang Z, Camprecios G, Stueck A, Dong H, et al. Mixed hepatocellular cholangiocarcinoma tumors: Cholangiolocellular carcinoma is a distinct molecular entity. *Journal of Hepatology.* 2017;66:952–961.
28. Xue R, Chen L, Zhang C, Fujita M, Li R, Yan S-M, et al. Genomic and Transcriptomic Profiling of Combined Hepatocellular and Intrahepatic Cholangiocarcinoma Reveals Distinct Molecular Subtypes. *Cancer Cell.* 2019;35:932-947.e8.
29. Sasaki M, Sato Y, Nakanuma Y. Cholangiolocellular Carcinoma With “Ductal Plate Malformation” Pattern May Be Characterized by ARID1A Genetic Alterations. *Am. J. Surg. Pathol.* 2019;43:352–360.
30. Wang A, Wu L, Lin J, Han L, Bian J, Wu Y, et al. Whole-exome sequencing reveals the origin and evolution of hepato-cholangiocarcinoma. *Nature Communications.* 2018;9:894.
31. Katz S-F, Lechel A, Obenauf AC, Begus-Nahrman Y, Kraus JM, Hoffmann EM, et al. Disruption of Trp53 in livers of mice induces formation of carcinomas with bilineal differentiation. *Gastroenterology.* 2012;142:1229-1239.e3.
32. Tschaharganeh DF, Xue W, Calvisi DF, Evert M, Michurina TV, Dow LE, et al. p53-dependent Nestin regulation links tumor suppression to cellular plasticity in liver cancer. *Cell.* 2014;158:579–592.
33. Yano H, Iemura A, Haramaki M, Momosaki S, Ogasawara S, Higaki K, et al. A human combined hepatocellular and cholangiocarcinoma cell line (KMCH-2) that shows the features of hepatocellular carcinoma or cholangiocarcinoma under different growth conditions. *J. Hepatol.* 1996;24:413–422.
34. Fujii H, Zhu XG, Matsumoto T, Inagaki M, Tokusashi Y, Miyokawa N, et al. Genetic classification of combined hepatocellular-cholangiocarcinoma. *Human pathology.* 2000;31:1011–7.
35. Roskams TA, Libbrecht L, Desmet VJ. Progenitor cells in diseased human liver. *Semin. Liver Dis.* 2003;23:385–396.
36. Yeh MM. Pathology of combined hepatocellular-cholangiocarcinoma. *J. Gastroenterol. Hepatol.* 2010;25:1485–1492.
37. Chen J, Li Y, Yu G. Diagnostic Value of Serum Biomarkers in Combined Hepatocellular-Cholangiocarcinoma. *J Coll Physicians Surg Pak.* 2020;30:263–267.

38. Potretzke TA, Tan BR, Doyle MB, Brunt EM, Heiken JP, Fowler KJ. Imaging Features of Biphenotypic Primary Liver Carcinoma (Hepatocolangiocarcinoma) and the Potential to Mimic Hepatocellular Carcinoma: LI-RADS Analysis of CT and MRI Features in 61 Cases. *AJR Am J Roentgenol.* 2016;207:25–31.
39. Mitchell DG, Bruix J, Sherman M, Sirlin CB. LI-RADS (Liver Imaging Reporting and Data System): summary, discussion, and consensus of the LI-RADS Management Working Group and future directions. *Hepatology.* 2015;61:1056–1065.
40. Jeon SK, Joo I, Lee DH, Lee SM, Kang H-J, Lee K-B, et al. Combined hepatocellular cholangiocarcinoma: LI-RADS v2017 categorisation for differential diagnosis and prognostication on gadoxetic acid-enhanced MR imaging. *European Radiology.* 2019;29:373–382.
41. Hwang J, Kim YK, Park MJ, Lee MH, Kim SH, Lee WJ, et al. Differentiating combined hepatocellular and cholangiocarcinoma from mass-forming intrahepatic cholangiocarcinoma using gadoxetic acid-enhanced MRI. *Journal of Magnetic Resonance Imaging.* 2012;36:881–889.
42. Nishie A, Yoshimitsu K, Asayama Y, Irie H, Aibe H, Tajima T, et al. Detection of Combined Hepatocellular and Cholangiocarcinomas on Enhanced CT: Comparison with Histologic Findings. *American Journal of Roentgenology.* 2005;184:1157–1162.
43. Willekens I, Hoorens A, Geers C, Op de Beeck B, Vandenbroucke F, de Mey J. Combined hepatocellular and cholangiocellular carcinoma presenting with radiological characteristics of focal nodular hyperplasia. *World J Gastroenterol.* 2009;15:3940–3943.
44. de Campos ROP, Semelka RC, Azevedo RM, Ramalho M, Heredia V, Armao DM, et al. Combined hepatocellular carcinoma-cholangiocarcinoma: report of MR appearance in eleven patients. *J Magn Reson Imaging.* 2012;36:1139–1147.
45. Fowler KJ, Sheybani A, Parker RA, Doherty S, M. Brunt E, Chapman WC, et al. Combined Hepatocellular and Cholangiocarcinoma (Biphenotypic) Tumors: Imaging Features and Diagnostic Accuracy of Contrast-Enhanced CT and MRI. *American Journal of Roentgenology.* 2013;201:332–339.
46. Li R, Yang D, Tang C-L, Cai P, Ma K-S, Ding S-Y, et al. Combined hepatocellular carcinoma and cholangiocarcinoma (biphenotypic) tumors: clinical characteristics, imaging features of contrast-enhanced ultrasound and computed tomography. *BMC Cancer.* 2016;16:158.
47. Sagrini E, Iavarone M, Stefanini F, Tovoli F, Vavassori S, Maggioni M, et al. Imaging of combined hepatocellular-cholangiocarcinoma in cirrhosis and risk of false diagnosis of hepatocellular carcinoma. *United European Gastroenterol J.* 2019;7:69–77.
48. Agrawal S, Belghiti J. Oncologic resection for malignant tumors of the liver. *Ann. Surg.* 2011;253:656–665.

49. Ma KW, Chok KSH. Importance of surgical margin in the outcomes of hepatocholangiocarcinoma. *World J Hepatol.* 2017;9:635–641.
50. Cucchetti A, Piscaglia F, Grigioni AD, Ravaioli M, Cescon M, Zanella M, et al. Preoperative prediction of hepatocellular carcinoma tumour grade and micro-vascular invasion by means of artificial neural network: A pilot study. *Journal of Hepatology.* 6;52:880–888.
51. Bagante F, Spolverato G, Weiss M, Alexandrescu S, Marques HP, Aldrighetti L, et al. Surgical Management of Intrahepatic Cholangiocarcinoma in Patients with Cirrhosis: Impact of Lymphadenectomy on Peri-Operative Outcomes. *World J Surg.* 2018;42:2551–2560.
52. Yoh T, Cauchy F, Soubrane O. Oncological Resection for Liver Malignancies: Can the Laparoscopic Approach Provide Benefits? *Ann. Surg.* 2020;
53. Holzner ML, Tabrizian P, Parvin-Nejad FP, Fei K, Gunasekaran G, Rocha C, et al. Resection of Mixed Hepatocellular-Cholangiocarcinoma, Hepatocellular Carcinoma, and Intrahepatic Cholangiocarcinoma: A Western Center Experience. *Liver Transpl.* 2020;
54. De Martin E, Rayar M, Golse N, Dupeux M, Gelli M, Gnemmi V, et al. Analysis of Liver Resection versus Liver Transplantation on Outcome of Small Intrahepatic Cholangiocarcinoma and Combined Hepatocellular-Cholangiocarcinoma in the setting of cirrhosis. *Liver Transpl.* 2020;
55. Lunsford KE, Court C, Seok Lee Y, Lu DS, Naini BV, Harlander-Locke MP, et al. Propensity-Matched Analysis of Patients with Mixed Hepatocellular-Cholangiocarcinoma and Hepatocellular Carcinoma Undergoing Liver Transplantation. *Liver Transpl.* 2018;24:1384–1397.
56. Sapisochin G, Javle M, Lerut J, Ohtsuka M, Ghobrial M, Hibi T, et al. Liver Transplantation for Cholangiocarcinoma and Mixed Hepatocellular-cholangiocarcinoma. Working Group Report from the ILTS Transplant Oncology Consensus Conference. *Transplantation.* 2020;
57. Kim JH, Yoon H-K, Ko G-Y, Gwon DI, Jang CS, Song H-Y, et al. Nonresectable combined hepatocellular carcinoma and cholangiocarcinoma: analysis of the response and prognostic factors after transcatheter arterial chemoembolization. *Radiology.* 2010;255:270–277.
58. Yoon Y-I, Hwang S, Lee Y-J, Kim K-H, Ahn C-S, Moon D-B, et al. Postresection Outcomes of Combined Hepatocellular Carcinoma-Cholangiocarcinoma, Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma. *J. Gastrointest. Surg.* 2016;20:411–420.
59. Na SK, Choi GH, Lee HC, Shin YM, An J, Lee D, et al. The effectiveness of transarterial chemoembolization in recurrent hepatocellular-cholangiocarcinoma after resection. *PLoS ONE.* 2018;13:e0198138.

60. Edeline J, Touchefeu Y, Guiu B, Farge O, Tougeron D, Baumgaertner I, et al. Radioembolization Plus Chemotherapy for First-line Treatment of Locally Advanced Intrahepatic Cholangiocarcinoma: A Phase 2 Clinical Trial. *JAMA Oncol.* 2019;
61. Malone CD, Gibby W, Tsai R, Kim SK, Lancia S, Akinwande O, et al. Outcomes of Yttrium-90 Radioembolization for Unresectable Combined Biphenotypic Hepatocellular-Cholangiocarcinoma. *J Vasc Interv Radiol.* 2020;
62. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc J-F, et al. Sorafenib in advanced hepatocellular carcinoma. *N. Engl. J. Med.* 2008;359:378–390.
63. Rizvi S, Khan SA, Hallemeier CL, Kelley RK, Gores GJ. Cholangiocarcinoma — evolving concepts and therapeutic strategies. *Nature Reviews Clinical Oncology.* 2017;15:95.
64. Kobayashi S, Terashima T, Shiba S, Yoshida Y, Yamada I, Iwadou S, et al. Multicenter retrospective analysis of systemic chemotherapy for unresectable combined hepatocellular and cholangiocarcinoma. *Cancer Sci.* 2018;109:2549–2557.
65. Salimon M, Prioux-Klotz C, Tougeron D, Hautefeuille V, Caulet M, Gournay J, 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.
66. Trikalinos NA, Zhou A, Doyle MBM, Fowler KJ, Morton A, Vachharajani N, et al. Systemic Therapy for Combined Hepatocellular-Cholangiocarcinoma: A Single-Institution Experience. *J Natl Compr Canc Netw.* 2018;16:1193–1199.
67. Lin C-C, Yang H-M. Fibrolamellar Carcinoma: A Concise Review. *Arch. Pathol. Lab. Med.* 2018;142:1141–1145.
68. Lalazar G, Simon SM. Fibrolamellar Carcinoma: Recent Advances and Unresolved Questions on the Molecular Mechanisms. *Semin. Liver Dis.* 2018;38:51–59.
69. Ramai D, Ofosu A, Lai JK, Gao Z-H, Adler DG. Fibrolamellar Hepatocellular Carcinoma: A Population-Based Observational Study. *Dig. Dis. Sci.* 2020;
70. Mayo SC, Mavros MN, Nathan H, Cosgrove D, Herman JM, Kamel I, et al. Treatment and prognosis of patients with fibrolamellar hepatocellular carcinoma: a national perspective. *J. Am. Coll. Surg.* 2014;218:196–205.
71. Njei B, Konjeti VR, Ditah I. Prognosis of Patients With Fibrolamellar Hepatocellular Carcinoma Versus Conventional Hepatocellular Carcinoma: A Systematic Review and Meta-analysis. *Gastrointest Cancer Res.* 2014;7:49–54.
72. Edmondson HA. Differential diagnosis of tumors and tumor-like lesions of liver in infancy and childhood. *AMA J Dis Child.* 1956;91:168–186.
73. Craig JR, Peters RL, Edmondson HA, Omata M. Fibrolamellar carcinoma of the liver: a tumor of adolescents and young adults with distinctive clinico-pathologic features. *Cancer.* 1980;46:372–379.

74. Yamashita S, Vauthey J-N, Kaseb AO, Aloia TA, Conrad C, Hassan MM, et al. Prognosis of Fibrolamellar Carcinoma Compared to Non-cirrhotic Conventional Hepatocellular Carcinoma. *J. Gastrointest. Surg.* 2016;20:1725–1731.
75. Stipa F, Yoon SS, Liau KH, Fong Y, Jarnagin WR, D'Angelica M, et al. Outcome of patients with fibrolamellar hepatocellular carcinoma. *Cancer.* 2006;106:1331–1338.
76. Mavros MN, Mayo SC, Hyder O, Pawlik TM. A systematic review: treatment and prognosis of patients with fibrolamellar hepatocellular carcinoma. *J. Am. Coll. Surg.* 2012;215:820–830.
77. Assi HA, Mukherjee S, Machiorlatti M, Vesely S, Pareek V, Hatoum H. Predictors of Outcome in Patients With Fibrolamellar Carcinoma: Analysis of the National Cancer Database. *Anticancer Res.* 2020;40:847–855.
78. Honeyman JN, Simon EP, Robine N, Chiaroni-Clarke R, Darcy DG, Lim IIP, et al. Detection of a recurrent DNAJB1-PRKACA chimeric transcript in fibrolamellar hepatocellular carcinoma. *Science.* 2014;343:1010–1014.
79. Cornella H, Alsinet C, Sayols S, Zhang Z, Hao K, Cabellos L, et al. Unique genomic profile of fibrolamellar hepatocellular carcinoma. *Gastroenterology.* 2015;148:806-818.e10.
80. Graham RP, Jin L, Knutson DL, Kloft-Nelson SM, Greipp PT, Waldburger N, et al. DNAJB1-PRKACA is specific for fibrolamellar carcinoma. *Mod. Pathol.* 2015;28:822–829.
81. Singhi AD, Wood LD, Parks E, Torbenson MS, Felsenstein M, Hruban RH, et al. Recurrent Rearrangements in PRKACA and PRKACB in Intraductal Oncocytic Papillary Neoplasms of the Pancreas and Bile Duct. *Gastroenterology.* 2019;
82. Vyas M, Hechtman JF, Zhang Y, Benayed R, Yavas A, Askan G, et al. DNAJB1-PRKACA fusions occur in oncocytic pancreatic and biliary neoplasms and are not specific for fibrolamellar hepatocellular carcinoma. *Mod. Pathol.* 2019;
83. Hirsch TZ, Negulescu A, Gupta B, Caruso S, Noblet B, Couchy G, et al. BAP1 mutations define a homogeneous subgroup of hepatocellular carcinoma with fibrolamellar-like features and activated PKA. *J. Hepatol.* 2019;
84. Nault JC, Fabre M, Couchy G, Pilati C, Jeannot E, Tran Van Nhieu J, et al. GNAS-activating mutations define a rare subgroup of inflammatory liver tumors characterized by STAT3 activation. *Journal of hepatology.* 2012;56:184–91.
85. Graham RP, Lackner C, Terracciano L, González-Cantú Y, Maleszewski JJ, Greipp PT, et al. Fibrolamellar carcinoma in the Carney complex: PRKAR1A loss instead of the classic DNAJB1-PRKACA fusion. *Hepatology.* 2018;68:1441–1447.

86. Riggle KM, Riehle KJ, Kenerson HL, Turnham R, Homma MK, Kazami M, et al. Enhanced cAMP-stimulated protein kinase A activity in human fibrolamellar hepatocellular carcinoma. *Pediatr. Res.* 2016;80:110–118.
87. Engelholm LH, Riaz A, Serra D, Dagnæs-Hansen F, Johansen JV, Santoni-Rugiu E, et al. CRISPR/Cas9 Engineering of Adult Mouse Liver Demonstrates That the Dnajb1-Prkaca Gene Fusion Is Sufficient to Induce Tumors Resembling Fibrolamellar Hepatocellular Carcinoma. *Gastroenterology.* 2017;153:1662-1673.e10.
88. Graham RP, Yeh MM, Lam-Himlin D, Roberts LR, Terracciano L, Cruise MW, et al. Molecular testing for the clinical diagnosis of fibrolamellar carcinoma. *Mod. Pathol.* 2018;31:141–149.
89. Torbenson M. Review of the clinicopathologic features of fibrolamellar carcinoma. *Adv Anat Pathol.* 2007;14:217–223.
90. Ganeshan D, Szklaruk J, Kundra V, Kaseb A, Rashid A, Elsayes KM, et al. Imaging features of fibrolamellar hepatocellular carcinoma. *AJR Am J Roentgenol.* 2014;202:544–552.
91. Lafaro KJ, Pawlik TM. Fibrolamellar hepatocellular carcinoma: current clinical perspectives. *J Hepatocell Carcinoma.* 2015;2:151–157.
92. Ichikawa T, Federle MP, Grazioli L, Madariaga J, Nalesnik M, Marsh W. Fibrolamellar hepatocellular carcinoma: imaging and pathologic findings in 31 recent cases. *Radiology.* 1999;213:352–361.
93. Friedman AC, Lichtenstein JE, Goodman Z, Fishman EK, Siegelman SS, Dachman AH. Fibrolamellar hepatocellular carcinoma. *Radiology.* 1985;157:583–587.
94. Palm V, Sheng R, Mayer P, Weiss K-H, Springfield C, Mehrabi A, et al. Imaging features of fibrolamellar hepatocellular carcinoma in gadoxetic acid-enhanced MRI. *Cancer Imaging.* 2018;18:9.
95. Pérez-Guillermo M, Masgrau NA, García-Solano J, Sola-Pérez J, de Agustín y de Agustín P. Cytologic aspect of fibrolamellar hepatocellular carcinoma in fine-needle aspirates. *Diagn. Cytopathol.* 1999;21:180–187.
96. Abdul-Al HM, Wang G, Makhlof HR, Goodman ZD. Fibrolamellar hepatocellular carcinoma: an immunohistochemical comparison with conventional hepatocellular carcinoma. *Int. J. Surg. Pathol.* 2010;18:313–318.
97. Ross HM, Daniel HDJ, Vivekanandan P, Kannangai R, Yeh MM, Wu T-T, et al. Fibrolamellar Carcinomas are Positive for CD68. *Mod Pathol.* 2011;24:390–395.
98. Pinna AD, Iwatsuki S, Lee RG, Todo S, Madariaga JR, Marsh JW, et al. Treatment of fibrolamellar hepatoma with subtotal hepatectomy or transplantation. *Hepatology.* 1997;26:877–883.

99. Atienza LG, Berger J, Mei X, Shah MB, Daily MF, Grigorian A, et al. Liver transplantation for fibrolamellar hepatocellular carcinoma: A national perspective. *J Surg Oncol.* 2017;115:319–323.
100. Ang CS, Kelley RK, Choti MA, Cosgrove DP, Chou JF, Klimstra D, et al. Clinicopathologic characteristics and survival outcomes of patients with fibrolamellar carcinoma: data from the fibrolamellar carcinoma consortium. *Gastrointest Cancer Res.* 2013;6:3–9.
101. Chakrabarti S, Tella SH, Kommalapati A, Huffman BM, Yadav S, Riaz IB, et al. Clinicopathological features and outcomes of fibrolamellar hepatocellular carcinoma. *J Gastrointest Oncol.* 2019;10:554–561.
102. Abou-Alfa GK, Mayer R, Venook AP, O’Neill AF, Beg MS, LaQuaglia M, et al. Phase II Multicenter, Open-Label Study of Oral ENMD-2076 for the Treatment of Patients with Advanced Fibrolamellar Carcinoma. *Oncologist.* 2020;
103. Simon EP, Freije CA, Farber BA, Lalazar G, Darcy DG, Honeyman JN, et al. Transcriptomic characterization of fibrolamellar hepatocellular carcinoma. *Proc. Natl. Acad. Sci. U.S.A.* 2015;112:E5916-5925.
104. Averill AM, Rehman HT, Charles JW, Dinh TA, Danyal K, Verschraegen CF, et al. Inhibition of the chimeric DnaJ-PKAc enzyme by endogenous inhibitor proteins. *J. Cell. Biochem.* 2019;120:13783–13791.
105. Studer LL, Selby DM. Hepatic Epithelioid Hemangioendothelioma. *Arch. Pathol. Lab. Med.* 2018;142:263–267.
106. Lau K, Massad M, Pollak C, Rubin C, Yeh J, Wang J, et al. Clinical patterns and outcome in epithelioid hemangioendothelioma with or without pulmonary involvement: insights from an internet registry in the study of a rare cancer. *Chest.* 2011;140:1312–1318.
107. Mehrabi A, Kashfi A, Fonouni H, Schemmer P, Schmied BM, Hallscheidt P, et al. Primary malignant hepatic epithelioid hemangioendothelioma. *Cancer.* 2006;107:2108–2121.
108. Weiss SW, Enzinger FM. Epithelioid hemangioendothelioma: a vascular tumor often mistaken for a carcinoma. *Cancer.* 1982;50:970–981.
109. Sardaro A, Bardoscia L, Petruzzelli MF, Portaluri M. Epithelioid hemangioendothelioma: an overview and update on a rare vascular tumor. *Oncol Rev.* 2014;8:259.
110. Ishak KG, Sesterhenn IA, Goodman ZD, Rabin L, Stromeyer FW. Epithelioid hemangioendothelioma of the liver: a clinicopathologic and follow-up study of 32 cases. *Hum. Pathol.* 1984;15:839–852.
111. Rosenberg A, Agulnik M. Epithelioid Hemangioendothelioma: Update on Diagnosis and Treatment. *Curr Treat Options Oncol.* 2018;19:19.

112. Tanas MR, Sboner A, Oliveira AM, Erickson-Johnson MR, Hespelt J, Hanwright PJ, et al. Identification of a disease-defining gene fusion in epithelioid hemangioendothelioma. *Sci Transl Med*. 2011;3:98ra82.
113. Tanas MR, Ma S, Jadaan FO, Ng CKY, Weigelt B, Reis-Filho JS, et al. Mechanism of action of a WWTR1(TAZ)-CAMTA1 fusion oncoprotein. *Oncogene*. 2016;35:929–938.
114. Errani C, Zhang L, Sung YS, Hajdu M, Singer S, Maki RG, et al. A novel WWTR1-CAMTA1 gene fusion is a consistent abnormality in epithelioid hemangioendothelioma of different anatomic sites. *Genes Chromosomes Cancer*. 2011;50:644–653.
115. Antonescu CR, Le Loarer F, Mosquera J-M, Sboner A, Zhang L, Chen C-L, et al. Novel YAP1-TFE3 fusion defines a distinct subset of epithelioid hemangioendothelioma. *Genes Chromosomes Cancer*. 2013;52:775–784.
116. Patel NR, Salim AA, Sayeed H, Sarabia SF, Hollingsworth F, Warren M, et al. Molecular characterization of epithelioid haemangioendotheliomas identifies novel WWTR1-CAMTA1 fusion variants. *Histopathology*. 2015;67:699–708.
117. Doyle LA, Fletcher CDM, Hornick JL. Nuclear Expression of CAMTA1 Distinguishes Epithelioid Hemangioendothelioma From Histologic Mimics. *Am. J. Surg. Pathol*. 2016;40:94–102.
118. Mulazzani L, Alvisi M. Imaging findings of hepatic epithelioid hemangioendothelioma and fibrolamellar hepatocellular carcinoma: a critical appraisal of current literature about imaging features of two rare liver cancers. *Translational Cancer Research*. 2018;8:S297-S310–S310.
119. Dong Y, Wang W-P, Cantisani V, D’Onofrio M, Ignee A, Mulazzani L, et al. Contrast-enhanced ultrasound of histologically proven hepatic epithelioid hemangioendothelioma. *World J Gastroenterol*. 2016;22:4741–4749.
120. Ganeshan D, Pickhardt PJ, Morani AC, Javadi S, Lubner MG, Elmohr MM, et al. Hepatic hemangioendothelioma: CT, MR, and FDG-PET-CT in 67 patients—a bi-institutional comprehensive cancer center review. *Eur Radiol*. 2020;30:2435–2442.
121. Virarkar M, Saleh M, Diab R, Taggart M, Bhargava P, Bhosale P. Hepatic Hemangioendothelioma: An update. *World J Gastrointest Oncol*. 2020;12:248–266.
122. Brahmabhatt M, Prenner S, Bittermann T. Liver transplantation for hepatic epithelioid hemangioendothelioma is facilitated by exception points with acceptable long-term outcomes. *Transplantation*. 2019;
123. Lerut JP, Orlando G, Adam R, Schiavo M, Klempnauer J, Mirza D, et al. The place of liver transplantation in the treatment of hepatic epithelioid hemangioendothelioma: report of the European liver transplant registry. *Ann. Surg*. 2007;246:949–957; discussion 957.

124. Lai Q, Feys E, Karam V, Adam R, Klempnauer J, Oliverius M, et al. Hepatic Epithelioid Hemangioendothelioma and Adult Liver Transplantation: Proposal for a Prognostic Score Based on the Analysis of the ELTR-ELITA Registry. *Transplantation*. 2017;101:555–564.
125. Konstantinidis IT, Nota C, Jutric Z, Ituarte P, Chow W, Chu P, et al. Primary liver sarcomas in the modern era: Resection or transplantation? *J Surg Oncol*. 2018;117:886–891.
126. Abreu P, Gorgen A, Oldani G, Hibi T, Sapisochin G. Recent advances in liver transplantation for cancer: The future of transplant oncology. *JHEP Rep*. 2019;1:377–391.
127. Chevreau C, Le Cesne A, Ray-Coquard I, Italiano A, Cioffi A, Isambert N, et al. Sorafenib in patients with progressive epithelioid hemangioendothelioma: a phase 2 study by the French Sarcoma Group (GSF/GETO). *Cancer*. 2013;119:2639–2644.
128. Sanduzzi-Zamparelli M, Rimola J, Montironi C, Nunes V, Avancini Ferreira Alves V, Sapena V, et al. Hepatic epithelioid hemangioendothelioma: an international multicenter study. *Digestive and Liver Disease*, accepted- In press.
129. Gigante E, Lai Q, Lerut JP, Nault J-C. Hepatic haemangioendothelioma: A proteiform disease. *Dig Liver Dis*. 2020;
130. Thway K, Doyle LA, Fukayama M et Hornick JL. Angiosarcoma. The 2019 WHO classification of tumours of the digestive system. Fifth Edition. Lyon (France) IARC. <http://publication.iarc.fr//579>.
131. Chaudhary P, Bhadana U, Singh R a. K, Ahuja A. Primary hepatic angiosarcoma. *Eur J Surg Oncol*. 2015;41:1137–1143.
132. Kim HR, Rha SY, Cheon SH, Roh JK, Park YN, Yoo NC. Clinical features and treatment outcomes of advanced stage primary hepatic angiosarcoma. *Ann. Oncol*. 2009;20:780–787.
133. Falk H, Herbert J, Crowley S, Ishak KG, Thomas LB, Popper H, et al. Epidemiology of hepatic angiosarcoma in the United States: 1964-1974. *Environ. Health Perspect*. 1981;41:107–113.
134. Popper H, Thomas LB. Alterations of liver and spleen among workers exposed to vinyl chloride. *Ann. N. Y. Acad. Sci*. 1975;246:172–194.
135. Pickhardt PJ, Kitchin D, Lubner MG, Ganeshan DM, Bhalla S, Covey AM. Primary hepatic angiosarcoma: multi-institutional comprehensive cancer centre review of multiphasic CT and MR imaging in 35 patients. *Eur Radiol*. 2015;25:315–322.
136. Locker GY, Doroshov JH, Zwelling LA, Chabner BA. The clinical features of hepatic angiosarcoma: a report of four cases and a review of the English literature. *Medicine (Baltimore)*. 1979;58:48–64.

137. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu, Clinical Practice Guideline Panel: Chair:, Panel members: EASL Clinical Practice Guideline: Occupational liver diseases. *J. Hepatol.* 2019;71:1022–1037.
138. Mundt KA, Dell LD, Crawford L, Gallagher AE. Quantitative estimated exposure to vinyl chloride and risk of angiosarcoma of the liver and hepatocellular cancer in the US industry-wide vinyl chloride cohort: mortality update through 2013. *Occup Environ Med.* 2017;74:709–716.
139. Przygodzki RM, Finkelstein SD, Keohavong P, Zhu D, Bakker A, Swalsky PA, et al. Sporadic and Thorotrast-induced angiosarcomas of the liver manifest frequent and multiple point mutations in K-ras-2. *Lab. Invest.* 1997;76:153–159.
140. Hollstein M, Marion MJ, Lehman T, Welsh J, Harris CC, Martel-Planche G, et al. p53 mutations at A:T base pairs in angiosarcomas of vinyl chloride-exposed factory workers. *Carcinogenesis.* 1994;15:1–3.
141. Marks EI, Pamarthy S, Dizon D, Birnbaum A, Yakirevich E, Safran H, et al. ROS1-GOPC/FIG: a novel gene fusion in hepatic angiosarcoma. *Oncotarget.* 2019;10:245–251.
142. Zheng Y-W, Zhang X-W, Zhang J-L, Hui Z-Z, Du W-J, Li R-M, et al. Primary hepatic angiosarcoma and potential treatment options. *J. Gastroenterol. Hepatol.* 2014;29:906–911.
143. Zeng D, Cheng J, Gong Z, Chen J, Long H, Zhu B. A pooled analysis of primary hepatic angiosarcoma. *Jpn. J. Clin. Oncol.* 2020;
144. Thampy R, Elsayes KM, Menias CO, Pickhardt PJ, Kang HC, Deshmukh SP, et al. Imaging features of rare mesenchymal liver tumours: beyond haemangiomas. *Br J Radiol.* 2017;90:20170373.
145. Maluf D, Cotterell A, Clark B, Stravitz T, Kauffman HM, Fisher RA. Hepatic angiosarcoma and liver transplantation: case report and literature review. *Transplant. Proc.* 2005;37:2195–2199.
146. Young RJ, Brown NJ, Reed MW, Hughes D, Woll PJ. Angiosarcoma. *Lancet Oncol.* 2010;11:983–991.
147. Tripke V, Heinrich S, Huber T, Mittler J, Hoppe-Lotichius M, Straub BK, et al. Surgical therapy of primary hepatic angiosarcoma. *BMC Surg.* 2019;19:5.
148. Orlando G, Adam R, Mirza D, Soderdahl G, Porte R, Paul A, et al. Hepatic Hemangiosarcoma: An Absolute Contraindication to Liver Transplantation—The European Liver Transplant Registry Experience. *Transplantation Journal.* 2013;95:872–877.

149. Tran Minh M, Mazzola A, Perdigao F, Charlotte F, Rousseau G, Conti F. Primary hepatic angiosarcoma and liver transplantation: Radiological, surgical, histological findings and clinical outcome. *Clin Res Hepatol Gastroenterol*. 2018;42:17–23.
150. Casali PG, Abecassis N, Aro HT, Bauer S, Biagini R, Bielack S, et al. Soft tissue and visceral sarcomas: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann. Oncol*. 2018;29:iv51–iv67.
151. Penel N, Bui BN, Bay J-O, Cupissol D, Ray-Coquard I, Piperno-Neumann S, et al. Phase II trial of weekly paclitaxel for unresectable angiosarcoma: the ANGIOTAX Study. *J. Clin. Oncol*. 2008;26:5269–5274.
152. Zhou Y-M, Sui C-J, Zhang X-F, Li B, Yang J-M. Influence of cirrhosis on long-term prognosis after surgery in patients with combined hepatocellular-cholangiocarcinoma. *BMC Gastroenterol*. 2017;17:25.
153. Okumura Y, Kohashi K, Tanaka Y, Kato M, Maehara Y, Ogawa Y, et al. Activation of the Akt/mammalian target of rapamycin pathway in combined hepatocellular carcinoma and cholangiocarcinoma: significant correlation between p-4E-BP1 expression in cholangiocarcinoma component and prognosis. *Virchows Arch*. 2020;
154. Cazals-Hatem D, Rebouissou S, Bioulac-Sage P, Bluteau O, Blanché H, Franco D, et al. Clinical and molecular analysis of combined hepatocellular-cholangiocarcinomas. *J. Hepatol*. 2004;41:292–298.
155. Graham RP, Yeh MM, Lam-Himlin D, Roberts LR, Terracciano L, Cruise MW, et al. Molecular testing for the clinical diagnosis of fibrolamellar carcinoma. *Mod. Pathol*. 2018;31:141–149.
156. Flucke U, Vogels RJC, de Saint Aubain Somerhausen N, Creytens DH, Riedl RG, van Gorp JM, et al. Epithelioid Hemangioendothelioma: clinicopathologic, immunohistochemical, and molecular genetic analysis of 39 cases. *Diagn Pathol*. 2014;9:131.
157. Theise N, Nakashima O, Park YN, Nakanuma Y. Combined hepatocellular-cholangiocarcinoma. in: F.T. Bosman, F. Carnoiro, R.H. Hrubá, N.D. Theise (Eds.) *WHO classification of tumors of the digestive system*. 2010;IARC Press, Lyon; 2010:225–227.

Figure 1

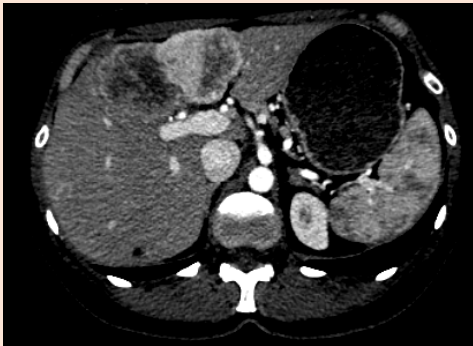
Epidemiology and risk factors

2-5% of primary liver cancer
Predominance of male
Cirrhosis: 20 to 50%
Risk factors: HBV, HCV, alcohol

Genetic alterations

TERT promoter 20 to 50%
TP53 25 to 49%
AXIN1 10%
ARID1A 8 to 15%
CTNNB1 6 to 10%
IDH1 5% *KRAS* 5%

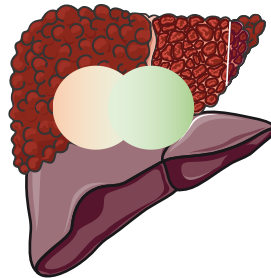
Imaging



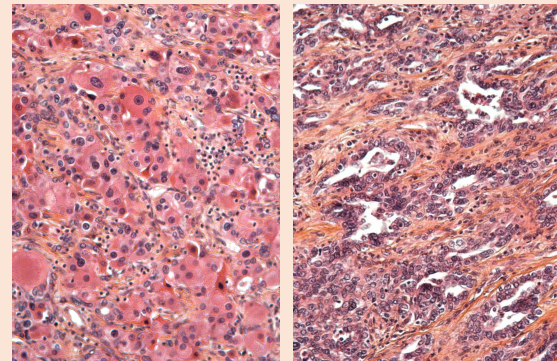
Major features

Delayed enhancing areas mixed with areas with arterial enhancement and washout
Capsular retraction, bile duct dilation and lymph nodes in HCC-like lesions
Venous invasion in iCCA-like lesions

Hepato-Cholangio carcinoma



Histology



HCC component CCA component

Major features

Presence of hepatocytic and cholangiocytic histology mixed with a transition or separated areas within the same tumor

Treatment

Liver resection+++

Transplantation: *clinical trial only*

TACE: *Not resectable, hypervascular and no metastasis*

Gemcitabin/platinum or sorafenib: *not resectable and hypovascular or with metastasis*

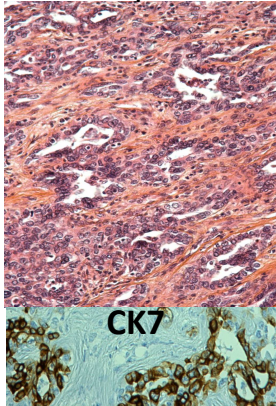
Figure 2

Hepato-cholangiocarcinoma

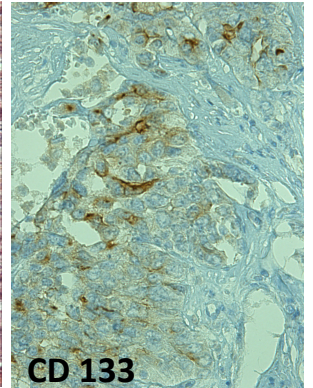
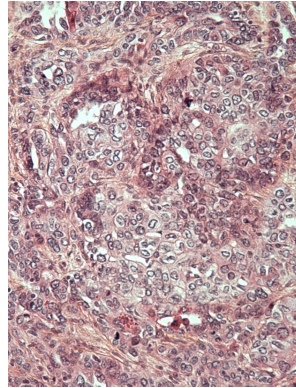
Combined HCC-CCA

HCC part

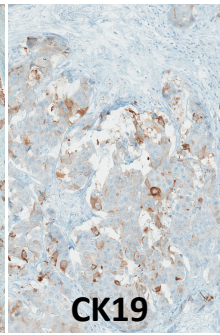
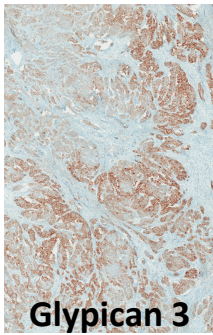
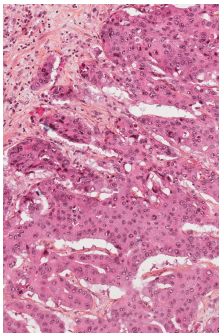
CCA part



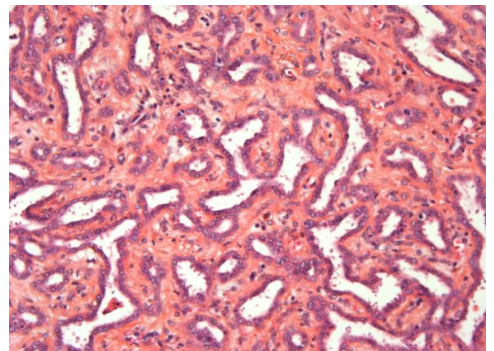
Intermediate cell carcinoma



HCC with stem cell features



Pure Cholangiolocarcinoma



Imaging features of hepato-cholangiocarcinoma

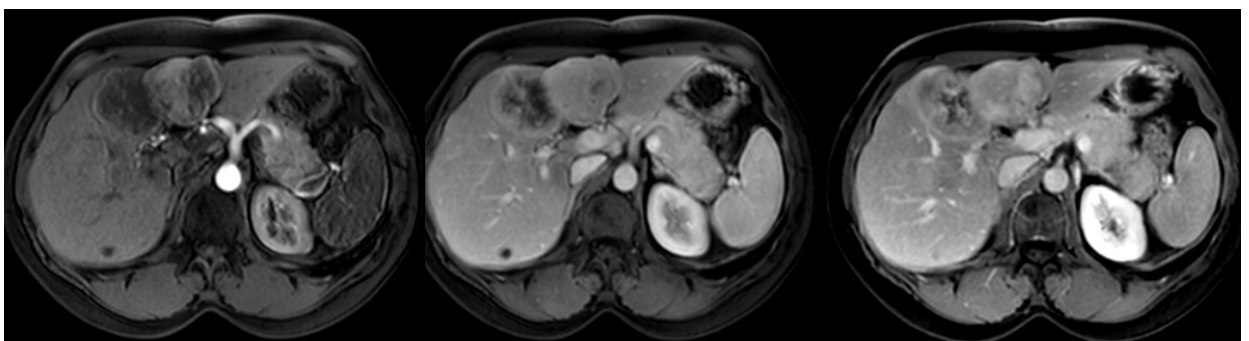
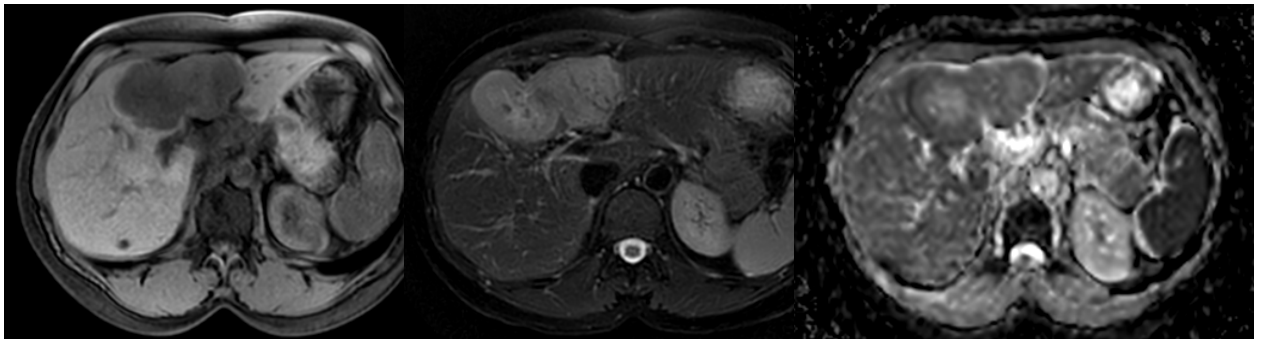


Figure 3

Epidemiology and risk factors

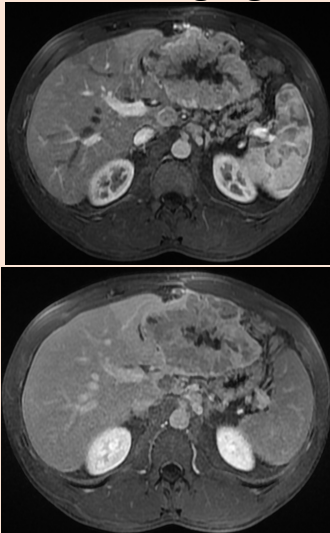
< 30 years old
Sex ratio 1/1
Normal Liver
No risk factors identified
Metastasis+++

Genetic alterations

DNJAB1 | PRKCA

DNJBA1-PRKCA fusion++++ (99-100%)
PRKAR1A germline inactivating mutations
(rare, Carney syndrome)

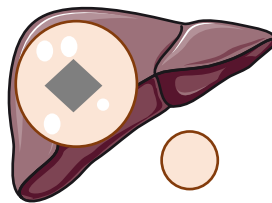
Imaging



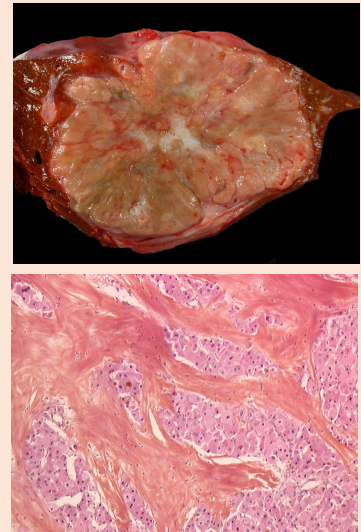
Major features

Lobulated tumor with stellate central areas with calcifications
Heterogeneous arterial phase hyperenhancement with delayed iso-hypo appearance
No fat, no venous invasion

Fibrolamellar carcinoma



Histology



Major features

Well-limited tumoral nodule with a fibrous scar
Large eosinophilic tumoral hepatocytes with fibrolamellar fibrous stroma

Treatment

Liver resection+++

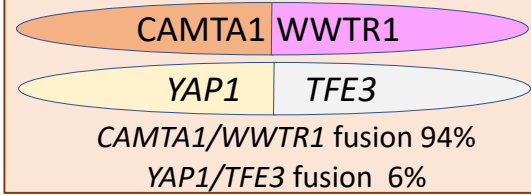
Transplantation: exceptionnally
Systemic chemotherapy?: Not resectable

Figure 4

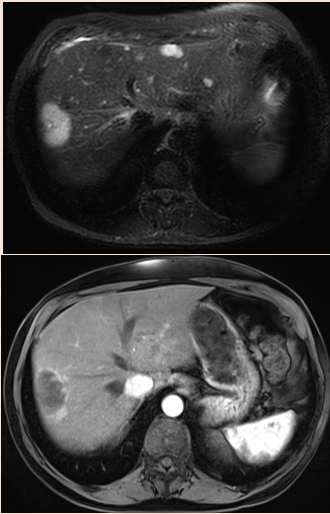
Epidemiology and risk factors

Prevalence < one/million
Normal liver
Female predominance
Frequent metastasis
Indolent to aggressive behaviour

Genetic alteration



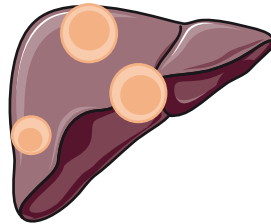
Imaging



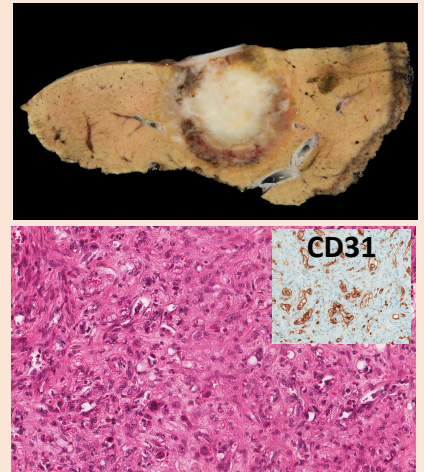
Major features

Multiple bilobar hypoattenuating subcapsular lesions
Halo/target enhancement
Capsular retraction.

Hepatic
Haemangio
endothelioma



Histology



Major features

Fibrous nodule with hyperhemic periphery
Epithelioid tumoral cells, mild atypias, cytoplasmic vacuoles
CD31 positive

Treatment

Liver resection: resectable disease

Transplantation++: multifocal progressive non resectable disease, extrahepatic metastasis is not a contre-indication

Surveillance: *indolent disease*

Systemic chemotherapy ?: *progressive disease, not resectable, not transplantable*

Figure 5

Epidemiology and risk factors

0.5-2.5 for 10,000,000 persons

Male predominance

Risk factors: vinyl chloride,
thorotrast, anabolic steroid ,
arsenic

Rarely on cirrhosis

Genetic alterations

KRAS mutation in sporadic cases

TP53 mutation in case due to
vinyl chloride

Few data available

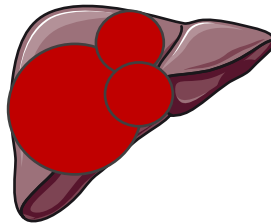
Imaging



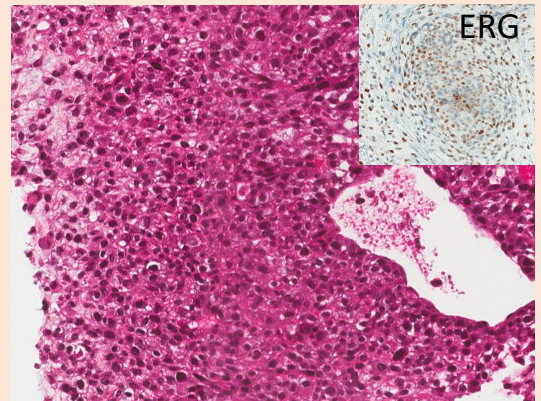
Major features

Multifocal large masses
Heterogeneous areas with
hemorrhage
Heterogeneous, nodular and
progressive enhancement

Hepatic
angiosarcoma



Histology



Major features

Highly cellular proliferation
Ill-defined spindle shaped-cells
Tumoral cells are erg positive
(nuclear staining)

Treatment

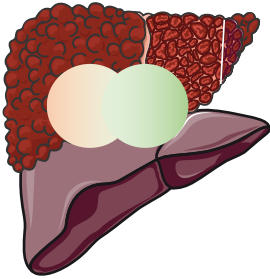
Liver resection++: resectable lesion

Transplantation: contra-indication

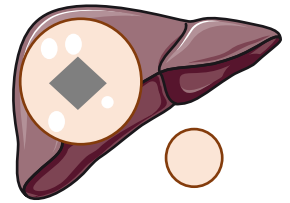
Systemic chemotherapy : *unresectable disease*

Graphical abstract

Hepato-cholangio
carcinoma

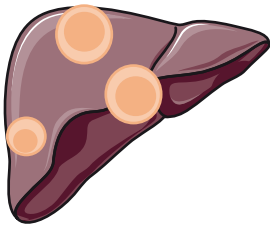


Fibrolamellar
carcinoma

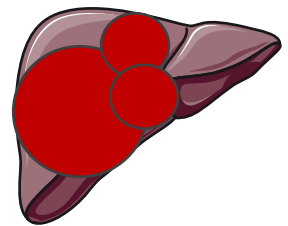


**Rare primary
liver cancers**

Hepatic
Haemangio
endothelioma



Hepatic
angiosarcoma



*Epidemiology
Risk factors
Imaging
Histology
Treatment*