Position Paper

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Rare primary liver cancers: An EASL position paper

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Summary

In recent years, owing to advances in our understanding of hepatocarcinogenesis, rare primary liver cancers (PLCs), including combined hepatocellular-cholangiocarcinoma, fibrolamellar carcinoma, and hepatic epithelioid hemangioendothelioma have garnered increased attention. In this position paper, an international panel of experts representing oncology, hepatology, pathology, radiology, surgery, and molecular biology has summarised the available information and evidence on the pathogenesis, diagnosis, and treatment of rare PLCs. While clinical trials of systemic treatments are underway for some rare PLCs, it is evident that more research, involving national and international collaboration, is required.

Introduction

In recent years, rare primary liver cancers (PLCs), including combined hepatocellular-cholangiocarcinoma (cHCC-CCA), fibrolamellar carcinoma (FLC), and hepatic epithelioid hemangioendothelioma (HEHE) have garnered increasing attention owing to an evolving understanding of molecular carcinogenesis in the liver and advances in therapeutic options for PLCs. Individually, most entities comprise less than 1-2% of all PLCs but taken together, rare PLCs constitute a clinically relevant percentage of all PLCs. Thus, to what extent treatment algorithms and new systemic options may be extrapolated to these rare PLCs is a question that increasingly arises at many multidisciplinary tumour boards. In this position paper, an international panel of experts representing oncology, hepatology, pathology, radiology, and surgery, has summarised the available information and evidence on the pathogenesis, diagnosis, and treatment of rare PLCs using a systematic approach. Based on our summary, we have derived concluding statements and algorithms to help guide the management of these patients. However, because of the lack of robust data in most areas, our position paper is not an evidence-based clinical practice guideline and consequently, no level of evidence and level of recommendation will be provided. Without doubt, more research, for example through international registries and cooperation within ERN Rare-Liver (European Reference Network on Rare Liver Diseases), is required to improve the management of rare PLCs. For some entities, clinical trials testing systemic treatments are underway; however, in other areas additional activities are necessary. This is especially true for the treatment of cHCC-CCA and FLC, since these patients have been excluded from international phase III trials in hepatocellular carcinoma (HCC).

Combined hepatocellular-cholangiocarcinoma

Histology and definition

Combined hepatocellular-cholangiocarcinoma (cHCC-CCA) is a PLC that, by definition, corresponds to a solitary tumour mass containing a hepatocellular component and a cholangiocellular component, both unequivocally identified under the microscope on H&E-stained slides (Fig. 1A).[1] Thus, cHCC-CCA is not the presence of HCC and cholangiocarcinoma (CCA) in a single patient in separate nodules. Macroscopically, cHCC-CCA lacks distinctive features and can solely be recognised through microscopic examination, requiring proper sampling adjusted to the tumour's size. All kinds of architectural patterns and cytological features that exist in HCC and CCA can be found.[1–4] No minimal proportion of each component is required to make the diagnosis.[1] While immunohistochemistry can corroborate biphenotypic differentiation, it cannot independently establish the diagnosis without prior detection of both components on H&E slides.[1,2] Immunohistochemical markers indicative of hepatocytic differentiation (mainly HepPar1 and Arginase-1) exhibit greater specificity than sensitivity, whereas markers of cholangiocytic differentiation (keratin 7 and keratin 19) are more sensitive than specific.[3] The two components can either be intermingled or close to each other and cancer stem cells can be seen in the transition area.[1] Nestin is a promising biomarker for the identification of cHCC-CCA and its expression correlates with worse clinical

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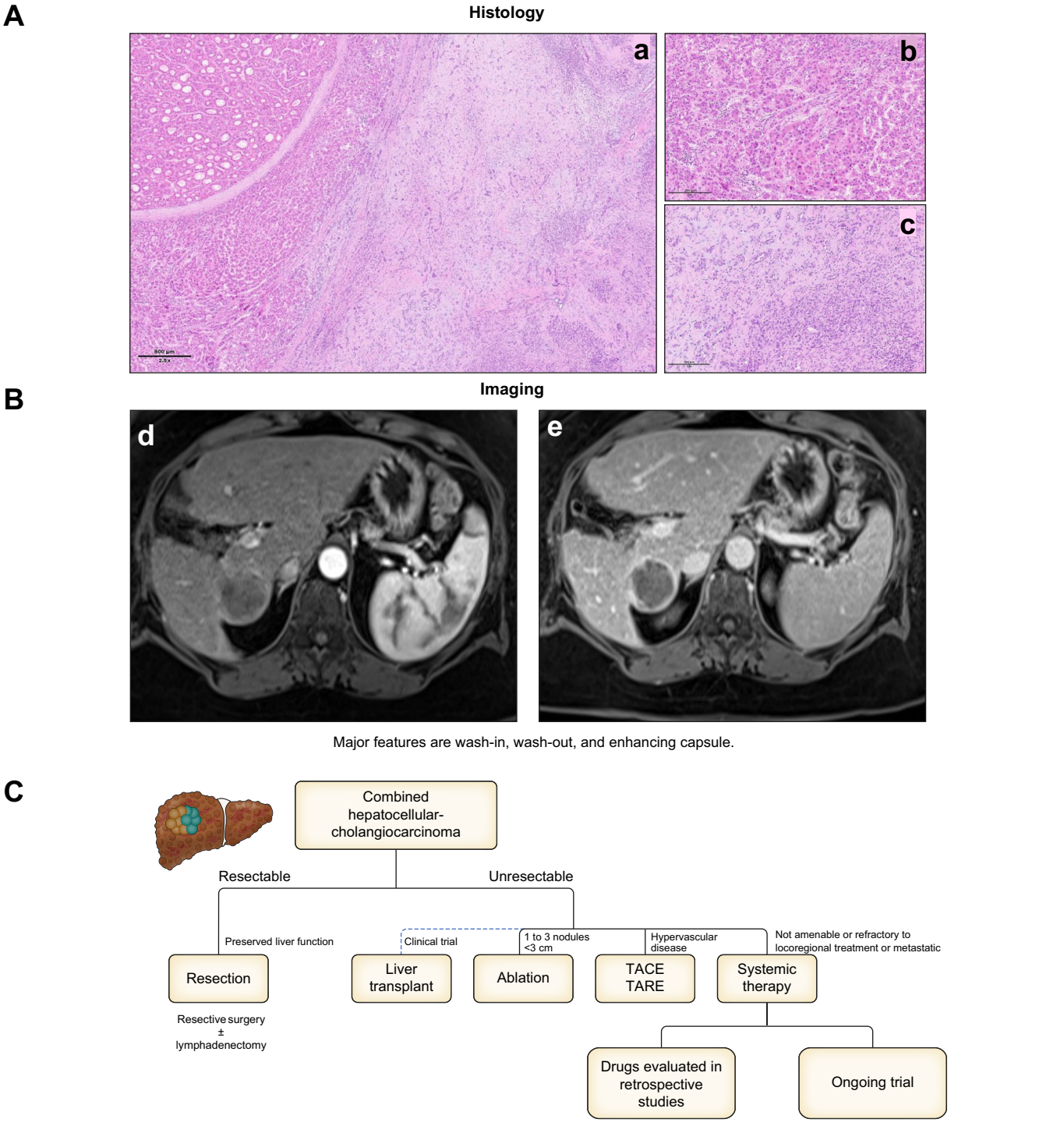

Fig. 1. Combined hepatocellular-cholangiocarcinoma: Main histopathological and imaging characteristics and treatment management. (A) Histological features. a) Microscopic features (H&E stain). At lower magnification (scale bar 500 μm), the tumour contains two different areas, one, on the left, with pseudoglandular and trabecular architectural features characteristic of hepatocellular carcinoma, and one, on the right, with small tubules scattered in a dense fibrous background, suggestive of cholangiocarcinoma. b) At higher magnification (scale bar 200 μm), the hepatocellular component is made of polygonal cells with an abundant eosinophilic cytoplasm and little stroma c) and the cholangiocellular component shows small tortuous ductular structures within a fibrotic stroma. (B) Imaging features. d) peripheral but no clear central enhancement (arterial phase), e) peripheral persistent hyperenhancement along with faint central wash out in portovenous phase. (C) Proposed algorithm for the management of patients with combined hepatocellular-cholangiocarcinoma. TACE, transarterial chemoembolisation; TARE, transarterial radioembolisation.

outcome.[5,6] In a subset of cases, the double phenotype is seen at the cellular level and the carcinoma looks homogeneous, made of uniform small cells, intermediate between hepatocytes and cholangiocytes.[7] In these very rare cases, immunohistochemistry is essential for recognising the double phenotype.[1] These PLCs are specifically called intermediate cell carcinomas. Undifferentiated carcinomas of the liver are epithelial tumours lacking specific morphological and immunohistochemical differentiation features.

Statement

- The diagnosis of cHCC-CCA is based on histology and requires the detection of both HCC and CCA components in one nodule. Nestin expression is associated with a worse prognosis. In very rare cases, the double phenotype is seen at the cellular level by immunohistochemical co-expression of hepatocyte and cholangiocyte markers. These very rare PLCs are termed intermediate cell carcinomas.

Epidemiology and risk factors

The prevalence of cHCC-CCA varies among different studies due to difficulties in terms of diagnosis and the evolution of its definition over time. According to the World Health Organization, cHCC-CCA accounts for 2-5% of all PLCs while population-based studies suggest a prevalence of only 1%.[1,8–10] cHCC-CCA primarily affects adults between the age of 60 and 65 years.[8,11–13] The sex distribution is similar to that of HCC, with male patients accounting for 70% to 80% of cases.[8,11–17] Along with male sex, cHCC-CCA shares other risk factors with HCC and CCA. In Eastern countries, hepatitis B virus infection represents the major risk factor, with frequencies exceeding 50% in most studies.[14,18–21] Conversely, risk factors like hepatitis C virus infection, metabolic dysfunction-associated steatohepatitis and alcohol-related steatohepatitis are more commonly reported in Western countries.[16,17,22,23] Compared to HCC, which occurs on a background of cirrhosis in 90% of cases, only 50% of cHCC-CCA cases in Western and Eastern countries develop in the presence of cirrhosis, probably due to relevant differences in inflammation-driven carcinogenesis and cellular origin.[16,17,19,24]

Statement

- cHCC-CCA account for 1% to 5% of all PLCs and develop in a cirrhotic liver in only 50% of cases.

Molecular biology

Several molecular studies have confirmed that cHCC-CCA are monoclonal tumours harbouring a median number of 60 to 70 non-synonymous coding mutations per tumour.[25–27] In terms of genetic alterations, both mutations in genes classically involved in HCC (telomerase reverse transcriptase [*TERT*] promoter, catenin beta 1 [*CTNNB1*]), in intrahepatic CCA (*KRAS*, isocitrate dehydrogenase 1 [*IDH1*] and fibroblast growth factor receptor 2 [*FGFR2*]) or in both tumours (*TP53* and BRCA1 associated protein-1 [*BAP1*]) have been identified in cHCC-CCA.[19,24–27] The percentage of *TERT* promoter mutations is around 25%, which is intermediate between intrahepatic CCA (6%) and HCC (50-60%).[25,28] However, it must be emphasised that the type and the frequency of mutations in driver genes in cHCC-CCA demonstrate significant variations according to available studies.[26]

Statement

- cHCC-CCA is a monoclonal tumour harbouring genetic alterations commonly identified either in HCC (*TERT* promoter, *CTNNB1*), in intrahepatic CCA (*KRAS*, *IDH1*, *FGFR2*), or in both tumour entities (*TP53*, *BAP1*).

Imaging features for diagnosis and staging

Unlike HCC in a patient with cirrhosis, specific radiological features enabling the diagnosis of cHCC-CCA have not been identified on computed tomography (CT) or magnetic resonance imaging (MRI) (Fig. 1B). A retrospective study evaluating the performance of LI-RADS (Liver Imaging Reporting And Data System) criteria in 61 patients with cHCC-CCA revealed that major criteria (arterial phase hyperenhancement and washout, enhancing capsule) could lead to misdiagnosis as HCC in over half of cases (54%), and that only taking LR-M targetoid or non-targetoid ancillary features into account (rim or peripheral arterial phase hyperenhancement, portal venous or delayed phase progressive central enhancement, liver surface retraction, marked diffusion restriction, or peripheral washout appearance) allows for classification of cHCC-CCA (88.5% of cases with cHCC-CCA displayed at least one ancillary feature).[29] Nevertheless, a distinct pattern enabling the differentiation of cHCC-CCA from other non-HCC malignancies has not been identified.[29] Elevated serum carbohydrate antigen 19-9 (CA19-9) and/or alpha-fetoprotein (AFP) are not reliable for cHCC-CCA diagnosis, although they could raise the suspicion of cHCC-CCA.

Statement

- Specific radiological features enabling the diagnosis of cHCC-CCA have not been identified.

Surgery and liver transplantation

Surgery represents the only curative treatment for cHCC-CCA[30,31] (Fig. 1C). Many factors may influence the feasibility of surgical intervention, such as the presence and severity of underlying liver disease, tumour size, and the presence of vascular invasion. cHCC-CCA is similar to HCC in terms of vascular involvement, and intrahepatic mass-forming CCA in terms of lymph node metastasis.[12] Surgical resection appears to lead to longer survival compared to non-surgical treatment, and major hepatectomy with wide resection margins seems the most appropriate approach.[30,32] The need for lymphadenectomy has not yet been determined[33,34]: the relative rarity of the disease and the diffuse lymphatic drainage of the liver do not allow for any strong recommendation. However, survival rates of patients resected for cHCC-CCA appear to be lower than for patients with HCC, with a mean disease free- and overall

survival (OS) of 13 and 31 months, respectively, suggesting that the clinical behaviour of cHCC-CCA is more similar to that of intrahepatic mass-forming CCA.[21]

Few studies have focused on patients with cHCC-CCA who underwent liver transplantation (LT) and the results are controversial, with conclusions in favour[35,36] and against[37,38] this indication. Well or moderately differentiated cHCC-CCA is associated with better post-transplant survival than poorly differentiated cHCC-CCA which accounts for the majority of cases.[35] The rarity of the disease, the lack of experience, and the controversial results do not allow for any strong recommendation.

Statement

- Surgical resection represents the only curative treatment for cHCC-CCA. The role of lymphadenectomy and LT is still unclear.

Locoregional treatment

Based on the complete remission rates after treatment of either HCC or CCA, local thermal ablation may be considered as an alternative curative-intent therapy for cHCC-CCA in tumours up to 3 cm[39,40] (Fig. 1C). Locoregional treatments have been studied in several retrospective small cohorts of patients with cHCC-CCA. Kim *et al.* reported responses (partial response or stable disease with >50% tumour necrosis) in 35 of 50 patients (70%) treated by transarterial chemoembolisation (TACE) and noted a strong association between response and arterial hyperenhancement.[41] Furthermore, the authors reported that survival after TACE was negatively associated with low tumour vascularity, high Child-Pugh class, and portal vein invasion when a multivariate analysis was performed.[41] A retrospective single-centre cohort of 22 patients with cHCC-CCA undergoing transarterial radioembolisation (TARE) reported an objective response rate (ORR) of 55% and disease control in 65%.[42] Lack of response to treatment, bilobar disease, presence of multiple tumours, and elevated CA19-9 were associated with poor survival.[42]

Statement

- Both TACE and TARE are viable options for tumour control in unresectable non-metastatic cHCC-CCA. Local thermal ablation is effective in tumours up to 3 cm.

Systemic treatment

There is no clear consensus on the optimal systemic treatment approach or the best candidate regimen in cHCC-CCA. In the clinical setting, patients with unresectable cHCC-CCA are often treated according to the guidelines for either HCC or CCA (Fig. 1C). We do not have randomised-controlled prospective studies, therefore clinical decision-making has to be based on retrospective data, which is subject to possible selection bias.[43–46] Table 1 outlines studies involving more than 10 patients.[11,47–52] Kim *et al.*[50] highlighted the selection bias present in many published studies. The authors compared patients treated with sorafenib and individuals receiving cytotoxic chemotherapy, exploring both first- and second-line treatments as well as other treatment types. As a result, the heterogeneous patient population, diverse cytotoxic chemotherapy regimens, and different treatment lines collectively contribute to selection bias, precluding its use as a basis for endorsing one approach over another. Notably, the number of patients with cirrhosis in the sorafenib group significantly differed from that in the cytotoxic chemotherapy group (p = 0.002), a key prognostic factor influencing patient outcomes.[50] Furthermore, cytotoxic chemotherapy encompasses various regimens, including platinum-based (such as gemcitabine plus cisplatin, fluoropyrimidines plus cisplatin, or adriamycin plus cisplatin) and non-platinum-containing cytotoxic chemotherapy (single-agent fluoropyrimidines or gemcitabine monotherapy). Given these considerations, it is essential to await the results of ongoing clinical trials before formulating recommendations. In this regard, there are two phase II studies focusing on patients with cHCC-CCA. The first is dedicated to second-line treatment and recently completed recruitment (NCT03230318). This phase II trial involves patients with unresectable advanced intrahepatic CCA and cHCC-CCA harbouring *FGFR2* gene fusions (determined by central laboratory fluorescence *in situ* hybridization [FISH]) or *FGFR2* gene mutations/amplifications (based on next-generation sequencing commissioned by the study centre). These patients will receive oral derazantinib capsules at 300 mg once daily, with the primary endpoint being ORR. The second phase II study (NCT05211323) is comparing the impact of adding bevacizumab and atezolizumab to gemcitabine and cisplatin (chemotherapy) *vs.* chemotherapy and atezolizumab in unresectable or advanced cHCC-CCA.

Statement

- Data on systemic treatments for unresectable cHCC-CCA are limited to retrospective series testing treatments recommended either for advanced HCC or CCA. Data from phase II trials specifically enrolling patients with cHCC-CCA are awaited. If enrolment in a clinical trial is not available, first-line systemic treatment validated for HCC and CCA are available options following discussion by a multidisciplinary tumour board.

Fibrolamellar carcinoma

Histology and definition

Fibrolamellar carcinoma (FLC), also known as fibrolamellar hepatocellular carcinoma,[53] is an exceptionally rare form of PLC that usually occurs in young patients without liver disease.[1] Macroscopically, FLC lesions are often large, well-delineated, and may mimic focal nodular hyperplasia (FNH) due to the abundance of fibrotic tissue that divides the tumour mass and converges in the centre creating a central scar-like appearance[1] (Fig. 2A). Histologically, FLC can be recognised by the abundant fibrotic stroma but mostly by the characteristic features of the tumour cells, which exhibit an abundant granular and strongly eosinophilic cytoplasm.[1,53,54] The stroma is organised in dense and thick fibrotic bundles around the cords of neoplastic cells, and focal calcification may be recognised.[1]

Table 1. Studies with focus on combined hepatocellular-cholangiocarcinoma involving more than 10 patients.

	Publications						
Author (year)	**Drug**	**Area/ country**	**Inclusion period**	**No. patients**	**Design**	**Outcome**	**Comments**
Salimon *et al.* (2017)[47]	Gemcitabine plus platinum-based CHT	France	2008 to 2017	30	Retrospective	OS, PFS	Descriptive
Kobayashi *et al.* (2018)[48]	Gemcitabine/cisplatin or fluorouracil/cisplatin or sorafenib or others	Japan	2002 to 2015	36		DCR, OS	Descriptive
Trikalinos *et al.* (2018)[49]	Gemcitabine plus 5-FU or gemcitabine plus platinum	USA	1999 to 2006	68		CDR, disease progression, OS, PFS	Selection bias
Kim *et al.* (2021)[50]	Sorafenib or cytotoxic CHT	Korea	1999 to 2015	99		ORR, OS, PFS	Selection bias
Gigante *et al.* (2022)[11]	Platinum-based therapy, TKIs or other CHT regimens	France	2009 to 2020	83		OS, PFS	Descriptive
Pomej *et al.* (2023)[51]	Cytotoxic CHT or non-cytotoxic CHT	Europe	2003 to 2022	44		OS, ORR	Selection bias
Jang *et al.* (2023)[225]	Nivolumab or pembrolizumab or atezolizumab plus bevacizumab or pilimumab plus nivolumab	Korea	2015 to 2021	25		OS, PFS	Descriptive
Gigante *et al.* (2023)[52]	Atezolizumab-Bevacizumab	France	2020 to 2022	16		ORR, OS, PFS	Descriptive
	Clinical trials						
ID/Sponsor	**Arms - Drug**		**Status**	**Estimated enrolment**	**Phase**	**Aim**	**Estimated study completion date**
NCT03230318; Basilea Pharmaceutica	Derazantinib single arm (iCCA and cHCC-CCA)		Completed	148 with *FGFR2* genetic alterations	II	ORR in advanced patients who received once per day at 300 mg of derazantinib capsules	2022
NCT05211323; National Cancer Institute	CHT plus atezolizumab *vs.* CHT plus bevacizumab and atezolizumab		Recruiting	88	II	PFS	2025

CHT, chemotherapy; DCR, disease control rate; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

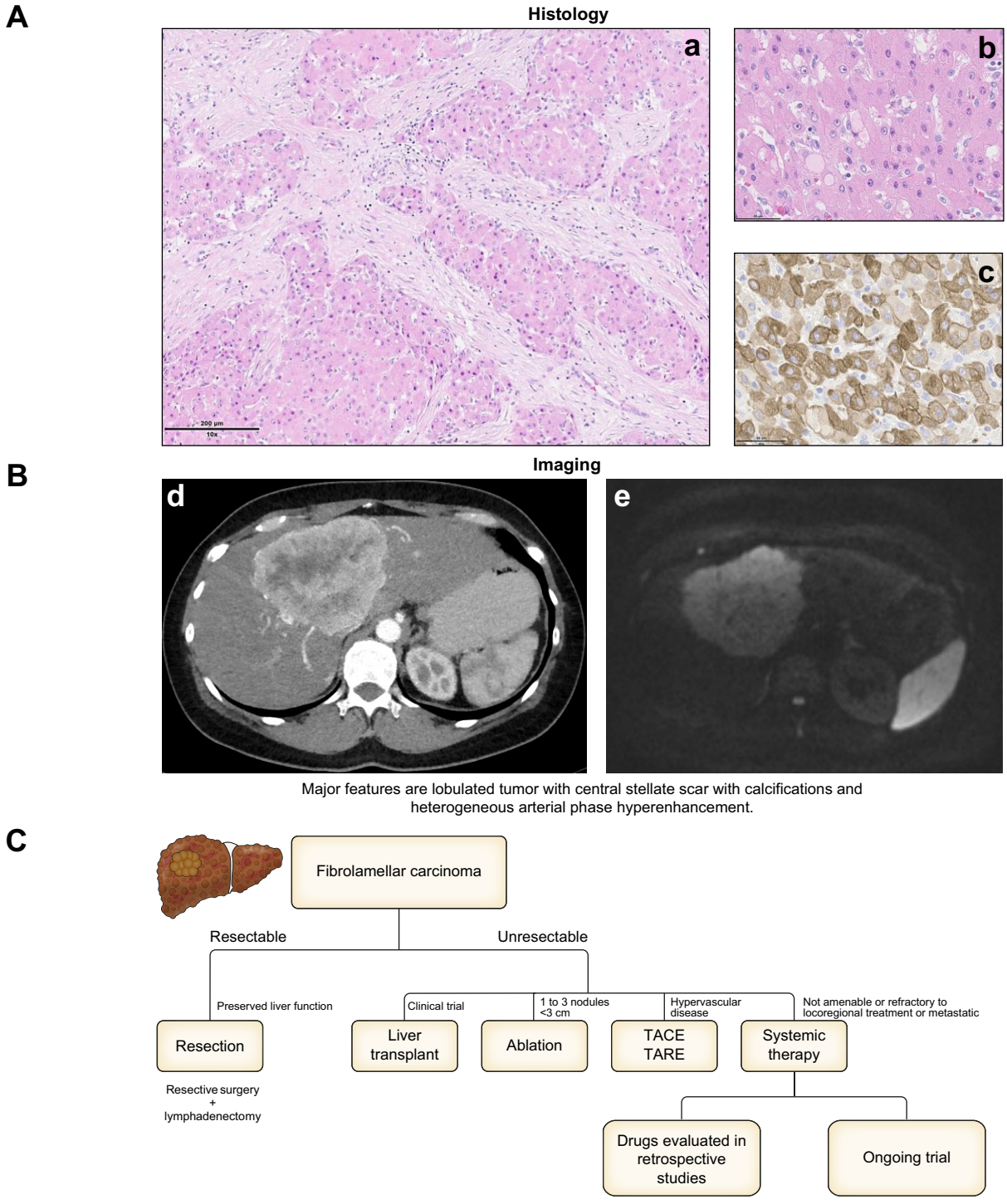

Fig. 2. Fibrolamellar carcinoma: Main histopathological and imaging characteristics and treatment management. (A) Histological features a) Microscopic features (H&E stain). Thick trabeculae of collagen partition the tumoral lesion that is made of large neoplastic cells showing a granular eosinophilic cytoplasm (scale bar 200 μm). b) A pale body is recognized, as well as other hyaline inclusions (scale bar 50 μm). c) Tumoral cells are diffusely positive for K7 (scale bar 50 μm). (B) Imaging features d) Heterogeneously enhanced lesion with lobulated margins and central stellate scar (arterial phase CT, e) Relatively high signal intensity in diffusion-weighted MRI. (C) Proposed algorithm for the management of patients with fibrolamellar carcinoma. TACE, transarterial chemoembolisation; TARE, trans-arterial radioembolisation.

The tumour cells, arranged in nests and clustered between the fibrotic lamellar bands, are large, polygonal, and have a centrally located vesicular nucleus and a prominent nucleolus.[1] Mitoses are rare, nuclear pleomorphism is low. Cytoplasmic inclusions are common and include so-called pale bodies which correspond to fibrinogen.[1] Fat accumulation and bile pigment are also observable.[1] FLCs are positive for hepatocytic markers, but, in contrast to HCC, the neoplastic cells frequently express keratin 7.[55,56]

Statement

- The diagnosis of FLC is based on histology from biopsies or surgical specimens requiring a well-defined tumour nodule composed of abundant dense fibrotic tissue and large tumoral hepatocytes with a granular eosinophilic cytoplasm. Diffuse keratin 7 expression can help to distinguish FLC from HCC.

Epidemiology and risk factors

FLC accounts for approximately 1% of PLCs[57,58] with a low incidence rate of 0.2 new diagnoses per million person-years.[59] FLC predominantly affects young adults, typically diagnosed between the ages of 20 and 30 years,[43] although some paediatric cases have been reported.[60] FLCs are equally distributed in both sexes, with a male-to-female ratio of 1:1, and without predilection for any particular ethnicity.[43,58] In contrast to HCC, the aetiology of FLC remains unclear. It usually develops on the background of a normal liver parenchyma without a history of viral hepatitis or metabolic dysfunction, and in the absence of underlying liver inflammation.[61,62] FLC is not associated with cirrhosis or chronic liver diseases and well-defined major risk factors for FLC have not been reported.[58,62,63]

Statement

- FLCs account for approximately 1% of all PLCs and usually occur in young non-cirrhotic adults.

Molecular biology

Almost all FLCs harbour a *DNAJB1-PRKACA* fusion – due to a focal deletion in chromosome 19.[64] This fusion gene is responsible for an oncogenic addiction through constitutive activation of the protein kinase A pathway.[65,66] Exceptional cases of FLC, without a *DNAJB1-PRKACA* fusion, have been described in patients with Carney complex due to germline inactivating mutations in *PRKAR1A*.[67] *DNAJB1-PRKACA* fusion can be detected either by FISH or PCR in clinical practice.[54] Even if the *DNAJB1-PRKACA* fusion is not fully pathognomonic of FLC, as the fusion can also be identified in oncocytic pancreatic and biliary neoplasms, the clinical presentation between these two entities is completely different and, consequently, the identification of a *DNAJB1-PRKACA* fusion in a solid mass-forming liver tumour is considered as pathognomonic of FLC.[68] One of the differential diagnoses is a subtype of HCC harbouring somatic mutations of *BAP1* and *PKA* activation because these tumours have a fibrolamellar-like pattern at histology, and they occur in patients in their forties, in both sexes and in the absence of classic HCC risk factors.[69]

Statement

- The presence of a *DNAJB1-PRKACA* fusion is pathognomonic of FLC if found in a mass-forming liver tumour. *BAP1* mutations define a specific subgroup of HCC with fibrolamellar-like histological features occurring in older patients.

Imaging features for diagnosis and staging

FLC usually presents as a large, heterogeneously enhanced lesion with lobulated margins and a central stellate scar, with or without calcifications[70] (Fig. 2B). In addition to these features in dynamic contrast-enhanced sequences, FLC shows a tendency towards high signal intensity on diffusion MRI.[71,72] In most patients with FLC, serum AFP is not elevated, thus it should not be used for the diagnosis of FLC. Although some other markers have been described such as B12-binding proteins, none of them has been validated.[73,74] Discriminating FLC from benign FNH is sometimes challenging because they can both display central scars. At imaging, FNH usually displays uptake of hepato-biliary contrast agent in late phase MRI, in contrast to FLC. Moreover, the apparent diffusion coefficient value in diffusion-weighted MRI is lower in FLC than in FNH.[75,76] However, despite some features to differentiate FLC and FNH, ultimately histology is necessary to confirm the diagnosis.

Statement

- No specific radiological pattern exists for FLC. FLC usually presents as a large, heterogeneously enhanced lesion with a central scar. Histology, either via biopsy or primary resection in cases with high suspicion and resectable tumours, is necessary for definitive diagnosis.

Surgery and liver transplantation

Patients with FLC often present with advanced disease which includes involvement of regional lymph nodes (30-50%) and distant metastasis (30-40%).[77] When feasible (*i.e.* in patients without cirrhosis), surgical resection represents the only curative treatment option (Fig. 2C). In a systematic review of 575 patients, Mavros *et al.* reported that the 5-year survival rate of patients who underwent resection of FLC was 70% compared to 0% among patients who did not undergo surgical resection.[78] Complete surgical resection with negative margins (R0) has been associated with improved long-term OS.[77] In addition to R0 resection, regional lymph node dissection is warranted because of the high incidence of lymph node metastasis (30%) and regional recurrence in patients with nodal disease.[79,80] Factors associated with a poor prognosis after surgical resection include lymph node metastasis, multiple tumours, metastatic disease at presentation, and vascular invasion.[81] Among patients presenting with these factors, recurrence is relatively common after resection with rates ranging from 40-

100%.[82] Therefore, close follow-up is required after resection. If recurrence is detected, repeat surgical resection may be warranted and has been associated with good results.[83]

While there are no established criteria, LT is reserved for patients with large/multiple FLCs that are not resectable in the setting of no extrahepatic disease. A UNOS (United Network for Organ Sharing) analysis of 63 patients who underwent LT demonstrated 1-year, 3-year, and 5-year OS rates of 96%, 80%, and 48%, respectively.[84] In a separate systematic review, the 1-year, 3-year, and 5-year OS rates after LT for FLC were reported to be 63-100%, 43-75%, and 29-55%, respectively.[85]

Statement

- Complete surgical resection and lymphadenectomy achieve 5-year OS rates of 70% and, if resection is not feasible, LT is an option in patients with unresectable FLC in the absence of metastases.

Locoregional treatment

Based on the complete remission rates achieved in HCC, local thermal ablation may be considered as an alternative curative therapy for FLC only in case of early diagnosis of a tumour ≤3 cm in size,[39] although locoregional treatment strategies have not been formally assessed in FLC[86] (Fig. 2C). In addition, since most tumours exhibit arterial hyperenhancement similar to typical HCC, TACE or TARE also represent an option in patients with unresectable tumours.[87–89]

Statement

- Locoregional therapy (*i.e.* TACE or TARE) may represent an option for unresectable FLC.

Systemic treatment

FLC has been excluded from all major therapeutic trials in HCC and consequently there are limited prospective data (Fig. 2C). The main studies and trials on systemic therapy in FLC are listed in Table 2. Cytotoxic chemotherapy has been regarded as the standard approach and the combination of 5-fluorouracil (5-FU) and alfa interferon has been evaluated in several studies.[81,90–92] Nine patients were included in a prospective phase II trial of 5-FU (200 mg/m^2/d for 21 days of a 28 day cycle) combined with subcutaneous recombinant interferon alfa-2b (rIFNα2b 4 MU/m^2 every 3 weeks).[90] Among the eight evaluable patients, five responded (62.5%) and a median OS of 23.1 months was reported. Two single-centre retrospective studies using this regimen have reported response rates of 32% and 37% among 25 and 8 patients, respectively.[81,91] The regimen has also been evaluated in combination with nivolumab in a single-centre retrospective study.[92] Only patients who received at least six cycles and had one follow-up scan were evaluated and there was considerable variation in the administration on 5-FU and interferon.[92] Despite these sources of potential bias, the response rate among 14 evaluable patients was 50%, suggesting a possible additional benefit of nivolumab in these patients. Based on the observation that mTOR

Table 2. Systemic therapy regimens for fibrolamellar carcinoma.

Author (year)	Design	Regimen	No. patients (evaluable)	ORR %	mPFS (months)	mOS (months)
Patt YZ *et al.* (2003)[90]	Phase II prospective	5-FU and rIFNα2b	9 (8)	62.5	NR	23.1
Kaseb AO *et al.* (2013)[81]	Non-randomised retrospective single centre	5-FU + IFN	25	32	NR	NR
		PIAF	8	0	NR	NR
		Capecitabine + IFN	9	0	NR	NR
Lamarca A *et al.* (2020)[91]	Retrospective single centre	5-FU + IFN	8	37.5	NR	38.6
Gottlieb S *et al.* 2021[92]	Retrospective single centre	5-FU and rIFNα2b plus NIV 3 mg/kg	22 (14)	50	9	NR
Maniaci V (2009)[226]	Retrospective single centre	Cisplatin containing regimens	8 (8)	25	NR	56
Abou-Alfa G *et al.* (2020)[95]	Phase II prospective multicentre	ENMD-2076 (anti-Aurora Kinase A inhibitor)	35	3	3.9	19
Abou-Alfa G *et al.* (2021)[94]	Phase II prospective multicentre	Neratinib	15	0	NR	NR
Dika IE *et al.* (2020)[93]	Randomised phase II	Everolimus	9	0	2.6	12.5
		Letrazole/leurolide	8	0	2.7	14
		Letrazole/leurolide plus Everolimus	9	0	2.4	10.6
Kent P *et al.* (2022)[96]	Retrospective single centre	Nivolumab and lenvatinib	14	43	NR	NR

5-FU, 5-fluorouracil; IFN, interferon; NIV, nivolumab; NR, not reported; ORR, objective response rate; OS, overall survival; PIAF, cisplatin, IFN, doxorubicin, and 5-FU; PFS, progression free survival; rIFNα2b, recombinant interferon alfa-2b.

and S6 kinase are overexpressed in 25% of cases and that FLC is sometimes associated with pregnancy or oral contraceptive use, everolimus, letrozole, and leuprolide were evaluated as single agents and in combination in a small randomised phase II trial.[93] A FLC cohort was included in the basket study of the pan-HER irreversible tyrosine kinase inhibitor neratinib.[94] Among the 15 patients recruited, no responses were observed.[94] The identification of the *DNAJB1-PRKACA* fusion gene as an oncogenic driver of FLC raised the possibility that inhibition of aurora kinase A might be an effective strategy, but a prospective multicentre trial of ENMD-2076 achieved only one response (3%) among 35 heavily pre-treated patients.[95] The low tumour mutational burden suggests that FLC is unlikely to benefit from immune checkpoint inhibitors alone and there have been no prospective studies reported to date. Nivolumab and lenvatinib have been evaluated in the neoadjuvant setting and a response rate of 43% was reported for the 14 patients treated.[96] A number of case reports have shown variable outcomes with a complete response reported for one patient treated with the combination of ipilimumab and nivolumab[97] but no response for two patients treated with atezolizumab and bevacizumab[98] or single agent pembrolizumab.[99]

Alternative approaches are being explored. Preclinical and initial clinical experience using *DNAJB1-PRKACA*-derived peptides has demonstrated the induction of persisting vaccine-induced *DNAJB1-PRKACA*-specific T-cell responses[100] and clinical trials are ongoing (NCT04248569). The anti-apoptotic protein BCL-XL has been found to be overexpressed in FLC compared to adjacent normal tissue and has been targeted using a proteolysis targeting chimera which selectively degrades BCL-XL via the VHL ubiquitin E3 ligase.[101] Pre-clinical studies have shown promising results in combination with irinotecan.[101]

Statement

- To date, the most used regimen for the systemic treatment of FLC is the combination of 5-FU and interferon, with response rates of 25-62.5%. New strategies are based on the evolving understanding of the biology of FLC.

Hepatocellular carcinoma on adenoma

Epidemiology, risk factors and molecular biology

Hepatocellular adenomas (HCAs) are rare primary benign liver tumours derived from hepatocytes. HCAs occur mostly in young women taking oral contraception (incidence of 3/100,000 women on oral contraception). Bleeding and malignant transformation are major complications observed in 10-20% and <5% of the cases, respectively.[102] HCAs can be divided into major molecular subgroups associated with specific risk factors and clinical behaviours: hepatocyte nuclear factor 1 alpha-inactivated mutated HCA, inflammatory HCA, β-catenin activated HCA with exon 3 or exon 7, 8 mutations of *CTNNB1* (b^{ex3}HCA or $b^{ex7,\ 8}$HCA), and sonic hedgehog HCA[103,104] (Table 3). Inflammatory HCA may also acquire *CTNNB1* mutations, resulting in mixed inflammatory-β-catenin HCA. Male sex and exon 3 mutations of *CTNNB1* in the tumour are the main risk factors for malignant transformation.[103] A two-step model explains the mechanism of malignant transformation of HCA to HCC in most cases with[1] the occurrence of mutations of *CTNNB1* in exon 3, and[2] telomerase reactivation mainly caused by *TERT* promoter mutation.[104] Of note, malignant transformation occurs also in other HCA molecular subgroups but with a lower incidence (40% of malignant transformation in b^{ex3}HCA *vs.* 4-5% in other molecular subgroups).[103] Mutations in exon 3 of *CTNNB1* can be detected either by molecular biology or by immunohistochemistry (glutamine synthase overexpression [sensitive and specific] and nuclear translocation of β-catenin [less sensitive but highly specific]).[103,105] A diagnosis of HCC on HCA requires either the presence of both components ("nodule in nodule"), or clinical information about a history of incompletely resected HCA at the same location.

Statement

- In patients with HCA, male sex and/or *CTNNB1* exon 3 mutations are associated with an increased risk of malignant transformation into HCC. Identification of *TERT* promoter mutations in HCA is frequently associated with malignant transformation.

Table 3. Description of the main molecular subgroups of HCA.

	Genetic alterations	Risk factors	Histology/IHC	Complications
HNF1A inactivated	Bi-allelic inactivating mutations of *HNF1A*	OC	Tumour steatosis, complete loss of LFABP in the tumour	Familial adenomatosis if germline *HNF1A* mutation
Inflammatory	*IL6ST, JAK1, STAT3, FRK, ROS1, GNAS*	Obesity, alcohol, OC	Inflammatory infiltrate, sinusoidal dilatation, dystrophic arteries, SAA and CRP diffuse expression in the tumour	Inflammatory syndrome Rare SAA amyloidosis
CTNNB1 mut. exon 3*	*CTNNB1* exon 3	Androgen, male	Cytological atypia, glutamine synthase homogeneous or heterogeneous diffuse overexpression and nuclear B-catenin in tumour	Malignant transformation
CTNNB1 mut. exon 7.8*	*CTNNB1* exon 7 or 8		Glutamine synthase patchy overexpression and no nuclear B-catenin in tumour	
Sonic hedgehog activated	*INHBE/GLI1* fusion	Obesity	Small monotonous hepatocytes, Haemorrhage	Bleeding

CRP, C reactive protein; CTNNB1, catenin beta 1; FABP, fatty acid-binding protein; GNAS, guanine nucleotide binding protein (G Protein), alpha stimulating activity polypeptide 1; HCA, hepatocellular adenoma; HNF1A, hepatocyte nuclear factor 1 A; INHBE, inhibin subunit beta E; IHC, immunohistochemistry; IL6T, interleukin 6 cytokine family signal transducer; JAK1, Janus kinase 1; OC, oral contraception; SAA, serum amyloid A; STAT3, signal transducer and activator of transcription 3.
**CTNNB1* mutated HCA are also inflammatory in half of the cases.

Imaging features for diagnosis and staging

Both HCA and HCC most commonly present as hyper-enhancing tumours on arterial phase. However, a wash out pattern in the porto-venous phase of contrast-enhanced CT or MRI facilitates HCC diagnosis.[106] Therefore, in patients with HCA under surveillance, changes in wash out patterns along with symmetric or asymmetric lesion growth are suggestive of malignant transformation.[106] Although there are no specific radiological features to detect the *CTNNB1*-mutated HCA subtype on imaging, preliminary data indicate that the uptake of gadoxetic acid during the hepatobiliary phase is associated with marked activation of the β-catenin pathway and could be used to identify b^{ex3}HCA.[102,107] Currently, liver biopsy is recommended.

Statement

- Specific radiological features for HCC on HCA are lacking. Changes in wash-out patterns along with symmetric or asymmetric lesion growth suggests malignant transformation of HCA.

Surgery and liver transplantation

Resection should be considered in patients with high-risk features, *i.e.* male patients, increasing size by >20% compared to baseline imaging, no reduction in size after 6 months of discontinuation of hormonal therapy in HCAs, β-catenin-activated subtype, imaging features suggestive of malignant transformation.[108,109] Complete surgical resection should be the goal. Hepatectomy for benign liver lesions such as HCA is generally safe with a perioperative mortality of less than 1% and severe morbidity of less than 10%.[110,111] Both open and minimally invasive approaches have been shown to be safe.[112] The number of HCA lesions (*i.e.* hepatic adenomatosis) and risk features are not correlated with HCA-related complications, so surgical decision-making in this patient population should be the same.[113] When patients have disseminated disease with one or two dominant high-risk HCAs, selective resection of these lesions can be performed, keeping the other lesions under surveillance. LT should generally be performed only in exceptional cases.[114] In particular, LT should be considered in patients who have multiple lesions that are highly suspicious for malignant transformation (b^{ex3}HCA) that cannot be removed by resection alone. Other rare indications for LT include the presence of recurrent HCA that cannot be re-treated by resection, the presence of HCA-related portosystemic venous shunts, or recurrent life-threatening HCA-related bleeding due to tumours that cannot be removed by resection alone.[115,116]

Statement

- Surgical indications for HCA-related HCC are the same as for HCC linked to other aetiologies, *i.e.* BCLC stage A and a single nodule >2 cm in size. LT is performed only in exceptional cases with multiple suspicious HCAs or if recurrent life-threatening complications are not amenable to resection alone.

Locoregional treatment

Both local ablation and locoregional intraarterial therapies are part of the therapeutic armamentarium proposed by guidelines for the management of HCC.[117,118] Treatment recommendations for HCC arising from HCA should be based on those recommendations.[118]

Statement

- Locoregional treatment of HCC developing on HCA is based on recommendations for HCC.

Systemic treatment

Although not specifically addressed in the international guidelines, HCC arising on HCA is susceptible to the same treatments as HCC arising on cirrhosis and/or other aetiologies, such as the new standard of care first-line treatment consisting of an anti-PD-L1 (programmed death ligand 1) and VEGFA (vascular endothelial growth factor A)-targeted antibodies or anti-PD-L1 and anti-CTLA-4 (cytotoxic T lymphocyte antigen 4) antibodies. Since *CTNNB1* mutations occur early in the transition from HCA to HCC[104] and approximately two-thirds of patients with HCC on HCA are β-catenin-activated,[119,120] β-catenin-targeted therapy may be a future option for these rare patients.

Statement

- Systemic treatment for HCC arising on HCA is based on recommendations for patients with HCC.

Hepatic epithelioid haemangioendothelioma

Histology and definition

Hepatic epithelioid hemangioendothelioma (HEHE) is a rare malignant vascular tumour of the liver first described by Ishak in a series of 32 patients.[121] Of note, epithelioid hemangioendothelioma can also arise in other organs such the lung or bone. Single or multiple, HEHEs range from small nodules to large masses that have a firm, white to grey appearance, macroscopically resembling CCA (Fig. 3A). Histologically, HEHEs demonstrate variable cellularity with a sclerotic, hypocellular centre and a much more cellular and blurred periphery with infiltrative margins. Within the lesion, there are remnants of partially obliterated portal tracts and central veins, while at the invasive front, tumour cells infiltrate the sinusoids between the liver cell plates.[1,122] The tumour cells – either isolated, or forming cords and small nests embedded in the fibro-hyaline, sometimes myxoid stroma – show variable aspects, mostly epithelioid with a pale cytoplasm, or signet-ring like with a lumen that may contain red blood cells, but also spindle or stellate cells. Nuclear pleomorphism and mitoses can be seen. By immunohistochemistry, their endothelial nature is recognised by positivity for CD31, CD34, ERG and factor VIII-related antigen, which help in the differential diagnosis with CCA. Most HEHEs are low-grade malignancies, so Ki67 expression is low. Nuclear CAMTA1 expression, a surrogate marker of the

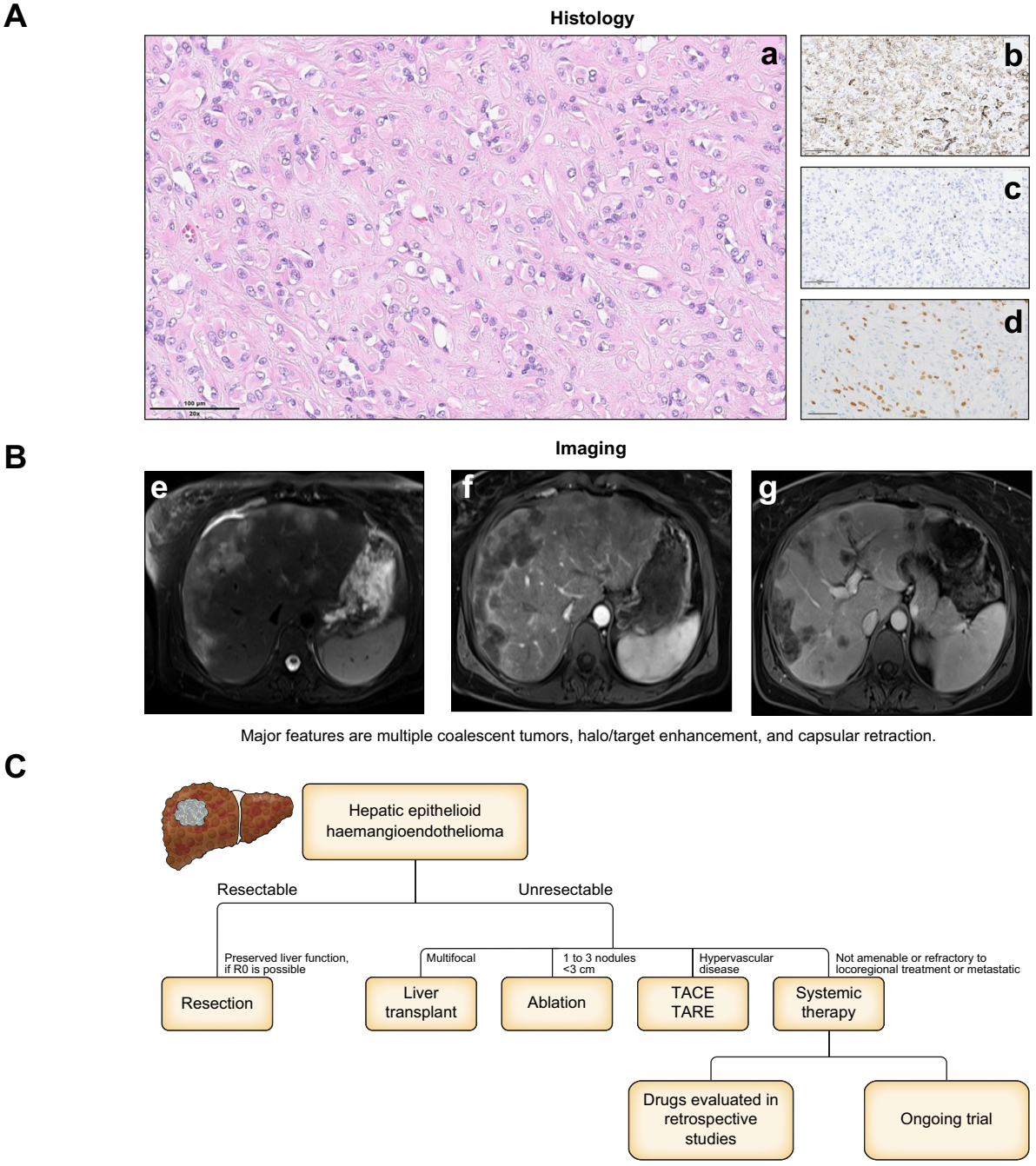

Fig. 3. Hepatic epithelioid hemangioendothelioma: Main histopathological and imaging characteristics and treatment management. (A) Histological features. a) Microscopic features (Scale bar 100 μm). On H&E stain, the tumour is made of epithelioid cells with a pale cytoplasm scattered in a hyaline stroma, or of signed-ring like cells with a vacuole that sometimes contains red blood cells. b) By immunohistochemistry the vascular nature of the tumoral cells is recognized on the CD34 stain, c) the proliferation is very low (Ki67 immunohistochemistry) d) and a nuclear CAMTA1 expression is observed. (B) Imaging features. e) subcapsular, coalescent lesion with retraction of hepatic surface. Target sign with concentric layers on T2-weighted image, f) hypointense lesions with peripheral enhancement in arterial phase, g) lollipop sign at portal phase image with tumour and obstructed hepatic vein ("candy and stick"). (C) We proposed an algorithm for the management of patients with hepatic epithelioid hemangioendothelioma. TACE, transarterial chemoembolisation; TARE, transarterial radioembolisation.

CAMTA1-WWTR1 fusion, is a highly sensitive and specific marker for HEHE, being positive in up to 86% of all cases.[123,124] Rare cases of centrolobular vein involvement with obstruction of hepatic venous outflow leading to Budd-Chiari syndrome have been described.[125]

Statement

- HEHE is a vascular tumour made of epithelioid cells showing variable cellularity with a sclerotic centre and infiltrative margins. Nuclear CAMTA1 expression is diagnostic in up to 86% of cases.

Epidemiology and risk factors

HEHEs account for less than 1% of PLCs, with an estimated incidence ranging from 0.1 to 1 case per 100,000.[121,126] Median age of presentation is between 35 and 45 years, spanning from 12 to 86 years in a large series of 137 cases.[122] HEHE is more commonly observed in women (ranging between 60-80% in different studies).[127,128] In terms of ethnicity, an analysis of the National Cancer Institute's SEER (Surveillance, Epidemiology, and End Results) database, which included 120 cases of HEHE, found a higher incidence in the white population.[129] The aetiology of HEHE remains unclear as no definitive risk factor has been confirmed. Several elements have been proposed as potential risk factors, including oral contraception, alcohol consumption, granulomatous diseases (sarcoidosis and Crohn's disease), vinyl chloride, asbestos, or thorotrast exposure, and viral hepatitis (hepatitis B and C) but none has been consistently demonstrated.[122,126,128,130]

Statement

- HEHE is more common in young adult women with normal liver and its aetiology remains unclear.

Molecular biology

Regardless of their localisation, all HEHEs harbour pathognomonic somatic genetic alterations. Approximately 90% of cases are defined by the presence of the *CAMTA1-WWTR1* gene fusion, that results from a translocation t(1;3) (p36.3;q25) and involves the calmodulin-binding transcription activator *CAMTA1*, and *WWTR1*, a TAZ-transcriptional coactivator. More rarely, a *YAP1-TFE3* fusion is detected.[131,132] These genetic alterations have never been detected in other types of tumours, including hepatic angiosarcoma (HAS), suggesting that they may serve as *bona fide* diagnostic criteria for HEHE. Of note, these fusions are also identified in HEHEs that develop outside the liver. *In vitro*, the *CAMTA1-WWTR1* gene fusion has been shown to activate the Hippo pathway through TAZ.[133] The *CAMTA1-WWTR1* gene fusion can be detected using PCR or FISH or, as reported above, indirectly via the nuclear overexpression of CAMTA1 on immunohistochemistry.[124,134]

Statement

- Presence of somatic *CAMTA1-WWTR1* or *YAP1-TFE3* fusions are pathognomonic of HEHE; the fusions are also detected in primary extrahepatic epithelioid hemangioendothelioma.

Imaging features for diagnosis and staging

There are no specific radiological features that characterise HEHE (Fig. 3B).[135] However, a recent study that included 740 lesions in 93 patients, reported that, in contrast to arterial hyperenhancement, a target sign with hyperdense inner rim in plain CT, as well as retraction of the liver capsule in lesions close to the liver margin are frequently found.[136] In addition, because of the vascular nature of the tumour, portal or venous branches ending at the tumour lesions, occur in 10-20% of tumours ("lollipop sign").[136] Most patients present with diffuse liver disease and a high proportion of coalescent tumours.[137] Metastases of other malignancies should be considered and excluded as a differential diagnosis to HEHE.[136,138]

Statement

- Specific radiological features for HEHE are lacking and therefore tumour biopsy is necessary. However, target sign and liver capsule retraction, as well as the "lollipop sign" from vascular structures ending at tumour lesions guide HEHE diagnosis.

Surgery and liver transplantation

Curative therapy for proven HEHE can be divided into three categories: surgical resection, LT, and minimally invasive ablative therapy like radiofrequency ablation via an open, laparoscopic or complete percutaneous approach (Fig. 3C). The goal of curative surgical treatment is to treat each tumour site in a manner that allows for adequate margins to prevent residual growth, recurrence, and/or metastatic occurrence. The choice of the appropriate therapy is highly dependent on the age and condition of the patient, the number of lesions, the location within the liver, and the quality and size of the future remnant liver. Adequate future remnant liver is needed to sustain postoperative regeneration of the liver after any therapy. A multidisciplinary team discussion preferably at a combined hepato-pancreato-biliary and transplant centre is advisable for these complex cases.

LT represents an established option in many countries. Resection is often challenging because HEHE often presents late with large lesions and multifocality. Considering the average age of patients with HEHE, complete resection may be indicated even when extreme resections are necessary.[139,140] ALPPS (associating liver partition with portal vein ligation for staged hepatectomy) has been described in the context of a case report.[141] Survival after resection seems to be similar to

that after LT, but cases are hardly comparable, because decisions are made on an individual basis.[140] In a study using data from the European Liver Transplant Registry, selected LT patients with resected extrahepatic spread (n = 41) displayed similar 5-year survival rates to patients without extrahepatic lesions receiving LT alone (n = 108) (82% *vs.* 72%).[142] To the best of our knowledge no randomised trials on HEHE and surgery exist. Hilar lymph node involvement and macrovascular ingrowth in final pathology specimens are considered independent factors for recurrence and poorer prognosis.[142]

Statement

- Both LT and surgical resection (with or without additional preoperative ablation) serve as options for HEHE with curative intent, with transplantation considered if complete resection is not feasible. Extrahepatic metastases do not represent an absolute contraindication to LT and resection.

Locoregional treatment

The vascular nature of HEHE renders most patients amenable to intraarterial tumour-targeted therapies (Fig. 3C). However, studies on locoregional treatments in HEHE are retrospective and limited to small cohorts. A recent paper evaluating the role of image-guided percutaneous ablation in patients with HEHE showed that up to 94.3% of ablated tumours did not progress and in cases where progression occurred, it manifested with lesions amenable to further ablation. The paper highlights the role of percutaneous ablation in the treatment of HEHE.[143]

In a series of 25 patients, four were treated exclusively by TACE whereas TACE was used for downstaging to LT in two patients.[144] No differences in OS were observed between patients treated with LT and those treated with TACE alone. Moreover, patients in whom TACE was used as a downstaging treatment achieved survival of 1-9 years.[144] The heterogeneity and limited size of patient cohorts prohibits clear recommendations. However, TACE could represent an additional treatment to curative surgical strategies or a palliative alternative.[145] At present, only one case report has been published on successful TARE in HEHE.[146]

Statement

- The vascular nature of HEHE renders most patients amenable to transarterial therapies, especially TACE. Intraarterial treatment options are discussed in case of limited extrahepatic (oligometastatic) disease that is refractory to or not suitable for surgery, ablation or stereotactic body radiation therapy.

Systemic treatment

According to the consensus document from ESMO (the European Society for Medical Oncology), in patients with localised, resectable HEHE, there is no evidence supporting the use of systemic therapies[147] (Fig. 3C). Moreover, active surveillance is the initial recommended option for cases presenting with asymptomatic locoregional or systemic metastases. Despite resection and LT being the most frequent treatment options, approximately 25% of patients receive systemic treatment during their lifetime.[126] However, consensus on the best systemic treatment options is lacking, especially since the current data is retrospective, as summarised in Table 4 (adapted from the ESMO consensus document published in 2021).[147] Therefore, we await the results of ongoing clinical trials. Current trials are evaluating various regimens: eribulin (microtubule targeting agent, NCT03331250), trametinib (MEK inhibitor, NCT03148275), gemcitabine plus pazopanib (CT+TKI, NCT01532687), and IK-930 (TEAD Inhibitor, NCT05228015).

Statement

- There is no consensus on the best systemic treatment options and treatment decisions are based on recommendations from a multidisciplinary tumour board.

Hepatic angiosarcoma

Histology and definition

Hepatic angiosarcoma (HAS) is a high-grade malignant vascular neoplasm and represents the most common sarcoma of the liver.[1,148] Grossly, HASs have variable appearance, from numerous poorly defined solid nodules to large spongy, necrotic, and haemorrhagic masses.[149] Histological differentiation is also variable, ranging from irregular and tortuous cavernous vascular spaces lined by protruding endothelial cells with hyperchromatic nuclei and filled with blood, to papillary protrusions within the sinusoids. When poorly differentiated, HAS consists of malignant spindle cells with pleomorphic and bizarre nuclei diffusely obliterating the sinusoids and forming hypercellular solid areas.[1,149] Mitoses are numerous and extramedullary haematopoiesis may be observed. The endothelial markers CD31, CD34, ERG and factor VIII-related antigen are positive, confirming the vascular lineage, but these markers may be less expressed in poorly differentiated HAS.[1,149] The high proliferation rate is confirmed by immunodetection of Ki67. P53 is overexpressed in most cases. These two features help to differentiate HAS from hepatic small vessel neoplasm, a recently described infiltrative vascular tumour thought to be a low-grade neoplasm.[150,151]

Statement

- HAS is the most frequent sarcoma of the liver and shows variable degrees of differentiation with frequent p53 overexpression and a high proliferation rate confirmed by immunodetection of Ki67.

Epidemiology and risk factors

HAS represents approximately 0.1-2% of all PLCs, with an estimated incidence of 0.5-2.5 cases per 10,000,000 individuals.[152] However, a recent analysis of the SEER database reported an increase in the number of cases over time.[153] HAS mainly affects adults, with a peak incidence in the sixth and seventh decades of life,[154] with a male to female ratio of 3-

Table 4. Major available series (>5 patients) on systemic treatments in advanced epithelioid haemangioendothelioma (adapted from Stacchiotti *et al.*).[147]

	Study type	Number of patients	CAMTA1/TFE3 assessment*	Regimens (n. patients)	Evidence of prior progression	Disease response	Median PFS (months)
Cioffi A *et al.* Journal of Clinical Oncology suppl. 2011	Multicentre, retrospective	34	No	Anthracycline (±ifosfamide) (16) Other cytotoxic (6) Sorafenib (6) Metronomic cyclophosphamide (2) Thalidomide (2) Imatinib (2)	No No No No No No	ORR = 0 ORR = 0 ORR = 0 BR = SD BR = SD BR = SD	4.8
Chevreau C *et al.* Cancer. 2013	Prospective, phase II	15	No	Sorafenib	Yes	ORR = 13% (2/15)	6
Agulnik M *et al.* Annals of Oncology. 2013	Prospective, phase II	7	No	Bevacizumab	No	ORR = 29% (2/7)	9
Yousaf N *et al.* Anticancer Research. 2015	Retrospective, single institution	19	No	IFN, weekly paclitaxel, 5-FU, caelyx, celecoxib, celecoxib + lenalidomide, doxorubicin, imatinib, carboplatin and paclitaxel, cyclophosphamide and vinblastine, axitinib, cyclophosphamide and etoposide, ifosfamide and doxorubicin, thalidomide, axitinib, pazopanib, semaxinib, sunitinib.	No	BR = PR (celecoxib, 1 patient); SD (other regimens)	NA
Kollar A *et al.* Acta oncologica. 2017	Retrospective analysis of prospective studies	10	No	Pazopanib	Yes	ORR = 20% (2/10)	26
Shiba S *et al.* BMC Cancer. 2018	Multicentre, retrospective	10	No	Carboplatin + paclitaxel + bevacizumab (CPB); paclitaxel; pazopanib; bevacizumab; streptozocine; cisplatin + epirubicin + bevacizumab (CEB)	No	BR = PR (CPB); SD (other regimens)	NA
Engel ER *et al.* J Pediatr Hematol Oncol. 2019	Multicentre, retrospective	6	Yes (1/6)	Sirolimus	Yes	ORR = 50% (3/6)	22
Sparber-Sauer M *et al.* Pediatr Blood Cancer. 2020.	Retrospective analysis of prospective studies	6	Yes	VAIA/VAC/CEVAIE, paclitaxel lenalidomide, INF, pazopanib	No	ORR = 0	NA
Stacchiotti S *et al.* Cancer. 2021	Multicentre, retrospective	38	Yes	Sirolimus (plasma level of 15-20 ng/dl)	Yes	ORR = 11% (4/37)	13
Frezza AM *et al.* Cancer Med. 2021	Multicentre, retrospective	73	Yes	Anthracycline-based (33) Weekly paclitaxel (11) Pazopanib (12) IFN-α 2b (15) Others (27)	Yes (19/33) Yes (6/11) Yes (10/12) Yes (12/15) Yes (24/27)	ORR = 3% (1/33) ORR = 9% (1/11) ORR = 0 ORR = 7% (1/15) NA	5.5 2.9 2.9 8.9 NA

BR, best response; NA, not available; NR, not reached; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.
*Immunohistochemistry or molecular testing.

4:1.[155] The aetiology of HAS remains unknown in approximately 75% of cases, while an association with specific risk factors can be found in the remaining 25%.[152,156] One of the most well-known risk factors is vinyl chloride monomer exposure.[157–159] The latency period between vinyl chloride exposure and the development of HAS is approximately 20 years, potentially explaining the slow gradual decline in diagnoses among highly exposed workers.[130,160] It is worth noting that HAS associated with vinyl chloride exposure can occur in the presence of cirrhosis, unlike in other cases.[161] Other identified risk factors include exposure to thorotrast,[162] androgenic steroids,[163] arsenic ingestion,[164] and exposure to radium.[165] Although rarely, additional risk factors such as urethane,[166] cyclophosphamide,[167] and oral contraceptive use,[168] have been described. Conversely, any involvement of viral hepatitis in HAS development has never been demonstrated.[153,169]

Statement

- Vinyl chloride exposure is a well-known risk factor for HAS and may lead to HAS after a latency period of up to 20 years.

Molecular biology

Very few data are available on the molecular pathogenesis of HAS. Old studies have reported *KRAS* mutations in vinyl chloride-related HAS, whereas more recent studies reported *TP53* mutations or mutations in mTOR pathway genes in sporadic HAS (*MTOR*, *PIK3CA*, *PTEN*).[170–172]

Statement

- Some studies reported *TP53* mutations or mutations in mTOR pathway genes in sporadic HAS.

Imaging features for diagnosis and staging

No specific feature enables the radiological diagnosis of HAS. On cross sectional imaging, this tumour may appear as a solitary mass or as multiple nodules or masses with heterogeneous and progressive enhancement.[173]

Statement

- No specific feature enables the radiological diagnosis of HAS.

Surgery and liver transplantation

Literature on surgery for HAS is extremely limited and for this reason recommendations are based exclusively on small retrospective series. Indeed, most patients are diagnosed with metastasis and/or extensive growth and are therefore not amenable to surgery. Surgery, usually combined with chemotherapy, is the only treatment that offers a very small chance of cure for patients with HAS. Resected patients tend to live longer (3.6, and 15 months)[174,175] than patients receiving best supportive care (1.3 months)[176] and long-term survival is probably limited to those patients who tolerate both surgery and chemotherapy.[177,178] Time between diagnosis and surgery should be limited as much as possible in the few patients who are eligible for resection. It is recommended that only resection with a free margin should be attempted.[176] Due to the very aggressive nature of HAS and its poor outcome, LT is not considered a viable therapeutic option.[179]

Statement

- Owing to the marked aggressiveness of HAS, surgery is rarely appropriate and is reserved for patients in whom a radical resection can be achieved. LT is not considered a viable option in patients with HAS.

Locoregional treatment

Reports on locoregional treatments either describe their role only in the management of HAS-related complications, such as embolisation in case of bleeding,[153] or are limited by their retrospective nature and low number of cases included.[173] TACE may be used to prevent fatal tumour rupture and massive haemorrhage, especially in patients with a large tumour burden.[175] The role of Yttrium-90-based TARE has been explored in a cohort of liver-dominant metastatic soft tissue sarcomas or primary hepatic sarcomas, including HAS.[180] Patients had a median liver progression-free survival of 9 months, and an ORR and disease control defined by mRECIST at 3 months of 56.7% and 80.0%, respectively.[180]

Statement

- Currently, locoregional treatments are mostly used in the management of HAS-related complications and there is no strong evidence to recommend TACE as an active treatment.

Systemic treatment

HAS has been included within trials of angiosarcoma (AS) more broadly, and AS in turn has often been included in trials for soft tissue sarcomas. Furthermore, HAS represent only 4% of ASs and are associated with a dismal prognosis.[181] Hence, the evidence base for systemic therapy in HAS is very poor and clinical practice is largely informed by therapeutic approaches applied in AS in general. The mainstay of therapy for AS is anthracycline- or taxane-based chemotherapy.[182,183] Pooled analysis of 11 prospective trials of anthracycline-containing therapy for soft tissue sarcomas identified 108 patients of whom 25% had a complete or partial response.[184] Median OS was 9.9 months and the combination of ifosfamide with doxorubicin was associated with better outcomes compared to single agent anthracycline.[184] Weekly paclitaxel was evaluated in a phase II trial in AS, with a reported response rate of 17%.[185] These data were confirmed in a subsequent study which combined 8 prospectively and 10 retrospectively included patients and reported a 35% ORR.[186] The Asian

Sarcoma Consortium reviewed therapy for AS and found that of 276 patients, 53% received first-line chemotherapy (paclitaxel in 68 patients and liposomal doxorubicin in 28) resulting in a median OS of 11.9 and 10.6 months, respectively, a statistically non-significant difference.[187]

Given the vascular nature of this tumour, anti-angiogenics have been explored. A small, randomised trial comparing weekly paclitaxel with and without bevacizumab failed to demonstrate any additional benefit for bevacizumab.[188] Patients with AS have also been included in trials evaluating kinase inhibitors and anti-VEGF therapy for soft tissue sarcomas with response rates of 11-14% for sorafenib, 0% for sunitinib and 12% for bevacizumab.[182] A retrospective study reported a 20% ORR among 40 patients with AS treated with pazopanib.[189]

There is limited data on immunotherapy, however, no responses were reported among the five patients with AS included in a prospective trial of durvalumab and tremelimumab for soft tissue sarcomas.[190] By contrast, in a small retrospective study including 25 patients, of whom 11 had visceral disease, an ORR of 18% was observed for single agent pembrolizumab.[191]

Statement

- Patients with advanced HAS have a poor prognosis but may derive some benefit from systemic therapy with anthracycline- or taxane-based chemotherapy. Anti-angiogenics have shown variable benefit and immunotherapy has yet to provide convincing evidence of efficacy in HAS.

Very rare primary liver cancers

Herein, we highlight the histological features, as well as limited clinical and outcome information, on some very rare PLCs. Primary hematolymphoid tumours of the liver are beyond the scope of this position paper.

Hepatoblastoma in adults

In 90% of cases, hepatoblastoma (HB) occurs in children under 5 years of age, representing the most common primary malignant liver tumour in the paediatric population, with an annual incidence of 0.5-1.5 per million.[192] Until the end of 2018, only 69 cases of adult HB had been reported, mostly with rather dismal prognosis due to late presentation with large liver mass and right upper quadrant pain, and high recurrence after surgery.[193] HB in adults is associated with cirrhosis in only 25% of cases.[194] Based on a review of 45 cases published until 2011, Rougemont and colleagues have identified marked differences between paediatric and adult cases, and thus, the existence of HB in adults remains controversial.[194] The main differential diagnosis in adults is HCC with significant histological overlap. As in children, the primary treatment for HB in adults is complete surgical removal. TACE has been used for the treatment of HB in both the neoadjuvant and palliative setting. In a small study involving 16 patients with HB, TACE was administered in one to three sessions, with tumour size reduction ranging from 19.0% to 82.0% and an average decrease in AFP values of 60.0%.[195] TACE facilitated subsequent complete surgical removal in 13 cases, and there were no significant adverse effects. Surgical specimens showed an average of 87% necrotic tissue, indicating that TACE, either alone or in combination with surgery, is an effective treatment option for HB. While this study primarily focused on infants and children, other reports suggest similar treatment effectiveness in adults. Since HB is sensitive to cytotoxic agents, such as cisplatin and doxorubicin,[196] neoadjuvant risk-adapted systemic therapy is recommended by the International Childhood Liver Tumor Strategy Group (SIOPEL, www.siopel.org). Further investigation is needed to confirm whether application of the paediatric HB protocol is beneficial in adult HB.

Mucinous cystic neoplasms

Mucinous cystic neoplasms (MCN) of the liver and biliary tract consist of multilocular cystic lesions without communication with the bile duct, lined by a cuboidal or columnar epithelium with variable quantities of mucin secretion, supported by an ovarian-like stroma expressing oestrogen and progesterone receptors on immunohistochemistry.[1] MCN are categorised as showing low grade or high grade dysplasia (previously named cystadenoma), or as associated with invasive carcinoma (previously named cystadenocarcinoma).[197–199] MCNs occur almost exclusively in women of various ages.[200] The presence of at least one major feature (tick septation, nodularity) and one minor feature (upstream biliary dilatation, thin septations, internal haemorrhage, perfusion change and <3 coexistent hepatic cysts) on MRI is suggestive of MCN.[201] Diagnosis of MCN with invasive carcinoma at imaging is challenging, although the presence of large mural nodules may indicate malignant transformation.[202] Both serum and cystic levels of CA19-9 or carcinoembryonic antigen could be elevated in simple biliary cysts, and in MCN with or without an invasive component, and are thus not useful for the differential diagnosis.[197,203,204] Surgical resection is the treatment of choice in MCN with dysplasia due to the risk of malignant transformation and for all MCNs with invasive carcinoma, resulting in a 5-year OS rate of 65-70%.[203,205,206]

Neuroendocrine neoplasms

Primary hepatic neuroendocrine neoplasms (PHNENs) include well-differentiated neuroendocrine tumours (NETs) and poorly differentiated neuroendocrine carcinomas (NECs).[1] They primarily affect adults aged 40-50 years and their diagnosis is challenging as symptoms are unspecific and radiological findings also lack specificity. Molecular data is limited; however, a study including 22 cases of PHNEN revealed that 14% harbour *TP53* and *SETD1B* mutations,[207] although alterations in *NOTCH3* and *BRD4* genes have also been described.[208] The histological findings for PHNENs are similar to those of NETs and NECs that develop in other organs with no liver-specific findings, and mixed neuroendocrine-non-neuroendocrine neoplasms with either a HCC or a CCA component have also been identified.[1] PHNENs are exceedingly rare and defining the primary nature requires careful exclusion of another primary location, as metastases are more frequent. Consequently, the diagnosis of PHNEN is based on the presence of a NET or NEC in the liver and the absence of any clinical, endoscopic, or imaging evidence for another site of origin.[209] Prognosis is better compared with HCC, with 5-year OS rates of 80%.[210] Surgery represents the cornerstone of PHNEN treatment.[211,212]

Carcinosarcoma

Hepatic carcinosarcoma (HCS) is a very rare (<1%) PLC composed of carcinomatous (either hepatocellular or cholangiocellular) and sarcomatous components. The sarcomatous part shows morphological and immunohistochemical evidence of a specific mesenchymal lineage. If the "sarcomatous" component is only showing a spindle cell morphology without specific proven mesenchymal differentiation, the tumour should be referred to as sarcomatoid HCC or CCA.[213] HCS affects primarily adult males at a median age of 61 years.[1,214] Pre-operative diagnosis of HCS is difficult, as imaging features are not specific, and biopsies frequently result in misdiagnosis.[215,216] Moreover, sarcomatous differentiation has been described for HCC and CCA even after treatment, complicating this diagnosis. Surgery represents the only treatment available with a median OS of 6 months.[215]

Liver squamous cell carcinoma

Primary squamous cell carcinoma of the liver is defined by the presence of morphological evidence of squamous differentiation and immunohistochemical reactivity for K5/6, p63, p40, K14 and K56 that indicate keratinized squamous epithelial origin.[217–219] However, immunohistochemistry alone is not sufficient to make the diagnosis, and a metastatic origin has to be excluded carefully. When primary, squamous cell carcinomas arise from the biliary epithelium and affect males at a ratio of 19:16 and a median age of 67 years.[218,219] Although surgery is sometimes feasible, the median OS is typically less than 12 months.[218]

Leiomyosarcoma

Primary leiomyosarcoma of the liver (LMS) originates from smooth muscle cells of intrahepatic vessels, bile ducts or the round ligament.[220,221] LMS arising from the inferior vena cava can be misleadingly considered as a primary of the liver. LMS can be observed in childhood and adulthood with a male-to-female ratio of 1:1.[222] Diagnosis is performed at histology when atypical spindle cells with eosinophilic cytoplasm and blunt ended nuclei growing in a fascicular pattern are found and other hepatic/extrahepatic tumours with spindle cell morphology have been excluded.[1,223] By immunohistochemistry, smooth muscle differentiation is confirmed by smooth muscle actin and, less frequently, desmin expression. Surgery represents the only curative treatment with a median OS of 19 months.[224]

Embryonal sarcoma

Embryonal sarcoma of the liver (ESL) is a primary malignant neoplasm unique to the liver observed mostly in children and rarely in adults. ESL presents as a large tumour composed of undifferentiated spindle or stellate cells and pleomorphic giant cells showing PAS-positive diastase-resistant inclusions. The immunophenotype is not specific with varying expression of keratin. Cells are haphazardly distributed in a fibromyxoid stroma.[1]

Conclusion and unmet needs

This position paper emphasises that our understanding of the pathophysiology and management of rare PLCs is still limited, with a lack of robust evidence for clinical application. The poor prognosis associated with most of these rare PLCs underscores the importance of coordinating clinical care and research efforts to address the primary unmet needs in this field. In terms of clinical management, a network of specialised clinicians, supported by multidisciplinary tumour boards dedicated to rare PLC, should be established at national or even international level (*e.g.* ERN Rare-Liver). Expert pathologists should also be integrated into this network to ensure a standardised pathological and immunohistochemical approach for confirming the diagnosis of these rare tumours. Furthermore, it is essential to facilitate access to sequencing platforms capable of conducting genomic analyses to identify the key genetic mutations characteristic of these cancers (such as *DNAJB1-PRKACA* fusion, *CAMTA1-WWTR1* fusion, etc.). This could prove invaluable in diagnosing challenging cases and searching for potentially targetable genetic alterations. Given the extremely low incidence of these cancers, international collaboration is imperative to facilitate the development of preclinical models, identify new therapeutic targets, establish retro- and prospective databases to better understand clinical behaviour, and create biobanks of serum, plasma, and tissue to identify new diagnostic, prognostic, and predictive biomarkers. Since most clinical trials testing new drugs in HCC or CCA typically exclude patients with rare PLCs, it is crucial to initiate dedicated phase II clinical trials on an international scale. This will ensure our ability to enrol enough patients for meaningful research outcomes. Lastly, fostering closer collaboration with patients and their families is essential to provide them with comprehensive information about their diseases and treatment options, as well as to involve them in the development of national networks and international research programmes.

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Abbreviations

5-FU, 5-fluorouracil; AS, angiosarcoma; BAP1, BRCA1 associated protein-1; CA19-9, carbohydrate antigen 19-9; cHCC-CCA, combined hepatocellular-cholangiocarcinoma; CCA, cholangiocarcinoma; CT, computed tomography; CTNNB1, catenin beta 1; FGFR2, fibroblast growth factor receptor 2; FISH, fluorescence *in situ* hybridization; HCA, hepatocellular adenoma; HCC, hepatocellular carcinoma; IDH1, isocitrate dehydrogenase 1; IFN, interferon; LT, liver transplantation; MRI, magnetic resonance imaging; ORR, objective response rate; OS, overall survival; PLC, primary liver cancer; PFS, progression-free survival; rIFNα2b, recombinant interferon alfa-2b; TACE, trans arterial chemoembolization; TARE, transarterial radioembolization; TERT, telomerase reverse transcriptase.

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Conflict of interest

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Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

HW and JCN suggested experts for the panel, which was then approved by the EASL governing board. All panel members discussed the outline of the position paper and prepared specific sections based on their medical and research speciality. CC compiled and arranged the manuscript. All authors conducted proofreading. Open questions and all statements were discussed in virtual conferences, and all authors approved the final version of the manuscript.

Supplementary data

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Author names in bold designate shared co-first authorship

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