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Hepatic epithelioid hemangioendothelioma: An international multicenter study

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ABSTRACT

Background and aims: Hepatic epithelioid hemangioendothelioma is an ultra-rare hepatic vascular tumor, diagnosed more frequently in females. The knowledge about this tumor derives mainly from small case series with sub-optimal treatment outcomes. The aim of this study is to identify the clinical and radiological issues helpful to develop an international prospective registry.
Methods: We conducted an international multicentric and retrospective study of patients with hepatic hemangioendothelioma. The clinical, pathological and radiological images collected during follow-up were reviewed. Central radiological revision was performed and 3 patterns of contrast were defined.
Results: Between 1994 and 2016, 27 patients with hepatic hemangioendothelioma were identified in three institutions but the final diagnosis was hepatic angiosarcoma in one. The majority were females, median age was 38.7-years and 17 patients were asymptomatic at diagnosis. ~~No patient had~~ Two out of ten (20%) patients had surgical specimens with positive macro-vascular invasion and 50% had extrahepatic disease, and the most frequent pattern was the progressive-central-contrast-uptake. After a median follow-up of 6.7-years, the 5- and 10-year survival rates are 91.5% and 51.9%, respectively.
Conclusions: This multicentric study shows the heterogeneous profile of patients with hepatic hemangioendothelioma, reflecting the need to establish a reference network in order to better characterize these patients and ultimately develop a personalized treatment strategy.

1. Introduction

Hepatic epithelioid hemangioendothelioma (HEHE) is a rare malignant vascular tumor of the liver of unknown etiology and a widely variable clinical course [1]. The incidence of HEHE is estimated between 0.1 and 1 cases per 100,000 population. It is more frequent in females (male to female ratio 2:3) with a median age of presentation between 35 and 45 years old and usually arises without any underlying liver disease [2]. The majority of the available data derive from single or small case series and two large co-

Abbreviations: HEHE, hepatic epithelioid hemangioendothelioma; CT, Computed Tomography; MR, Magnetic Resonance; RECIST, Response Evaluation Criteria In Solid Tumors; OS, Overall Survival; LR, Liver Resection; LT, Liver Transplantation; IFN-a, Interferon-alpha; RFA, Radiofrequency; ELTR, European Liver Transplant Registry; MVI, Macrovascular Invasion; UNOS, Using the United Network for Organ Sharing; VEGF, vascular endothelial growth factor.

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horts that have been reported by Makhlouf HR et al. [3]. and the European Liver Transplant Registry (ELTR) [4]. However, their analysis is primarily focused on pathological samples in the former and on transplanted patients only in the latter. Consequently, as is the case with other rare cancers, HEHE is poorly known and presents sub-optimal treatment outcomes due to a lack of robust knowledge and of recognized reference centers focused on this disease. In addition, this rare tumor receives no specific support or advocacy around the world.

The present study is an international analysis that aims to characterize the profile of patients with HEHE, analyze the prognosis and treatment approach in three different institutions and explore potential factors predicting patient outcome.

2. Patients and methods

Patients with the diagnosis of HEHE from Hospital das Clínicas - University of São Paulo School of Medicine, Brazil, Universidade Federal da Bahia, Salvador da Bahía, Brazil, and from Hospital Clinic of Barcelona between May 1994 and June 2016 were retrospectively analyzed. All patients who were diagnosed with HEHE with available baseline demographic, biochemical and clinical data, as well as histological and radiological data, were included in the study. The diagnosis followed the updated definitions of histopathological criteria, the images were centrally revised and the clinical/biochemical data were extracted from clinical reports. Patients were treated according to the local expertise of each institution. This study was approved by the Institutional Ethics Committee (HCB/2015/0605).

2.1. Pathology

Material for pathological and immunohistochemical analysis was obtained from surgical specimens (liver resection or liver transplantation), needle biopsy (liver, lymph nodes or metastases) or "wedge-biopsy". Hematoxylin and eosin (H&E) staining of formalin-fixed paraffin embedded (FFPE) tissue section of HEHE was evaluated by three expert pathologists (MS, CM and VAFA). The diagnosis was based on the presence of nodules composed of single or aligned epithelioid and histiocytoid cells intermixed with fibrous or myxoid stroma. These cells were sometimes detected lining vessels with the structure of veins or sinusoids. Atypical flat or epithelioid cells presenting intracytoplasmic capillary lumina, sometimes containing blood cells, were also considered for diagnosis. At immunohistochemistry (IHC) CD31 and CD34 are highly expressed by these cells, usually found concomitantly with factor-VIII related antigen (FVIII-Ag). The intracytoplasmic capillaries are highlighted with these endothelial markers. Histological features, nuclear atypia, angiolymphatic invasion, vascular occlusion by the tumor and the presence of papillary intravascular growth of the tumor, the presence of solid and spindle cell areas, as well as the number of mitosis present in 50 high power fields (HPF) were assessed. In addition, proliferation index of the tumor was assessed with Ki67 staining. For the IHC study, 4micron-thick sections were mounted on FLEX IHC microscope slides and pre-treated in PT-LINK (Dako, Glostrup, Denmark). All the antibodies were ready to use. The staining procedure was performed on the Autostainer Link 48 and Omnis Dako systems.

2.2. Central validation of images

Central reading of radiological images was performed for both dynamic contrast-enhanced Computed Tomography (CT) and Magnetic Resonance (MR). Given the retrospective and multicentric nature of the study, equipment changed during the time span covered by the study. For MR images, common sequences reviewed were single shot fast spin echo T2-weighted sequences and pre-contrast and dynamic 3D-T1 gradient-echo with fat saturation. Sequences among different equipment were considered comparable. Radiologic tumor response was based on the RECIST version 1.1 [5].

Table 1
Baseline characteristics of the patients and characteristics of the tumor.

Age, median [IQR][a] (years)	38.7 [23.8–45.1]
Male/Female, n	8/16
Liver disease, yes/no n	5/19
Breast injury, yes/no n	5/19
Symptoms at diagnosis, yes/no n	7/17
Type of symptoms:	
• Abdominal pain	2
• Dyspnea	1
• Dyspepsia	1
• Ascites	1
• Jaundice	1
• FUO[b]	1
HEHE[c] characteristics	
Multinodular disease n, (%)	16 (66.7)
Uninodular disease n, (%)	5 (20.8)
Confluent/diffuse n, (%)	3 (12.5)
Extrahepatic diseases n, (%)	12 (50)
Lymph node involvement n, (%)	3 (12.5)
Macrovascular invasion n, (%)	2 (8.4)

[a] Interquartile Range.
[b] FUO: Fever of Unknown Origin.
[c] HEHE: hepatic epitelioid hemangioendothelioma.

2.3. Statistical analysis

Continuous data were presented as median and interquartile interval (IQR), and categorical data were presented as frequency and percentages. Continuous variables were compared using U-Mann Whitney's test and, in case of more than two groups, the Kruskal-Wallis test was used. Categorical variables were compared using the Chi squared test or Fisher's exact test when appropriate. Overall survivals (OS) were calculated using the Kaplan–Meier method and by median times with their IQR from diagnosis until death or last follow-up date. All statistical analyses were performed using SAS software v9.4® and we considered a two-sided type I error = 5%.

3. Results

3.1. Demographic characteristics and clinical presentation

A total of 27 patients with the diagnosis of HEHE were identified in the patient reports of the three Institutions but only 25 of them had complete available information (demographic, laboratory and clinical data) and were included in the analysis (Flow-chart of the study, supplementary Fig. 1). Table 1 describes the baseline characteristics of this cohort. One of the 25 patients, after an initial needle biopsy suggestive of HEHE, was diagnosed with hepatic angiosarcoma in the liver explant and thus, excluded from the analysis. The majority of patients were females (66.7%), median age was 38.7 years (IQR 23.8–45.1) and only 5 (20%) patients had underlying chronic liver disease: 2 (8%) had hepatitis C virus (HCV) ~~liver~~ cirrhosis, 2 (8%) had liver steatosis and 1 (4%) had alcoholic cirrhosis.

At the time of diagnosis, 17 (68%) patients were asymptomatic. In one of those patients, a single HEHE nodule of 7 mm was incidentally diagnosed in the liver explant after liver transplantation for hepatocellular carcinoma (HCC). Right upper abdominal pain was the only symptom at diagnosis in 2 patients. However, 5 pa-

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tients presented ascites, dyspnea, dyspepsia, jaundice and fever of unknown origin lasting for 2 years, respectively.

3.2. Pathological data

All patients included in the study had a pathological diagnosis of HEHE in their center but the retrospective histopathological evaluation was available in 20 cases. In 10 cases the diagnosis was obtained by biopsy (1 wedge biopsy), while in the other 10 patients, the tissues were obtained from explanted livers ($n=4$) or resected tissues ($n=6$). Macroscopically, the lesions assumed the appearance of firm, well-defined, rubbery tan grey masses measuring between 0.4 and 12 cm without overtly hemorrhagic or necrotic areas. Tumor was multinodular in 11/20 patients. Two transplanted patients had regional lymph-node involvement and portal invasion, while an additional patient who received surgical resection had only lymph-node disease.

Microscopically, the tumors were composed of polygonal epithelioid cells with eosinophilic cytoplasm with focal intracytoplasmic capillary lumina. Most of the nodules had a growth pattern with infiltrative margins. In 9 out of the 20 patients (45%), the tumor showed solid architectural areas. Spindle-cell areas were observed in 3 patients (15%) constituting more than 50% of the total tumor burden, in 6 (30%) patients these represented between 25–50% of the tumor mass and in 11 (55%) patients they represented less than 25% of the tumor. Epithelioid cells infiltrating sinusoids and terminal hepatic venules (papillary growth) were observed in 13 (65%) patients and vascular vein occlusion was observed in 8 (40%) patients.

All patients showed less than 3 mitosis / 50 HPF and 8 (40%) presented high grade nuclear atypia. The expression of Ki67 was $\geq$10% in 3 patients (15%; 2 cases 10%, one >15%), >1% in 4 patients (20%; 2 cases >2% and 2 cases 1–2%) and <1% in 13 cases (65%). The diagnosis was confirmed by immunohistochemistry and specifically CD31 and CD34 were positive in 20/20 and 17/17 patients respectively, while Factor VIII was positive in 6/6 patients.

3.3. Imaging

Fourteen patients had been evaluated by CT and 10 by MR. Twelve out of the initial 24 patients (50%) presented extrahepatic disease at diagnosis, all but one with lung involvement (Table 1) and none with macro-vascular invasion (MVI). The most frequent radiological presentation was multinodular in 16 (66.7%) patients, uninodular in 5 (20.8%) and confluent or diffuse in 3 (12.5%).

Thirteen patients were centrally reviewed (7 received MR and 6 a CT). Here, HEHE was multinodular in 7 patients (54%), confluent in 3 patients (23%) and uninodular in 3 patients (23%). The tumor affected both hepatic lobes in 9 (69.2%) patients and 4 of these (30.8%) were initially detected as an extrahepatic tumor. Lymph node involvement was not observed at CT or MR. Nodules were subcapsular (at least one lesion in contact with the hepatic surface) in the majority of cases (9, 69.2%). Median diameter at the time of diagnosis was 26 mm (IQR 24–39 mm) and 16.5 mm (IQR 10–38 mm) for the first and second largest target lesions, respectively. Only in 2 (15.4%) of the patients, liver capsule retraction was reported and no ~~macrovascular invasion (MVI)~~ was observed by imaging techniques.

Among the 7 patients with central revision analysis with baseline MR, all HEHE showed hypointensity on pre-contrast T1-weighted sequences, and hyper or isointensity on T2-weighted sequences in all target lesions in 2 and 5 patients, respectively. All the lesions of the remaining 6 patients with baseline CT scan presented hypodense lesions.

Interestingly, in 87.5% of the patients all the lesions of each patient showed a similar contrast enhancement pattern. The majority of the lesions showed a slight centripetal enhancement from the arterial to portal phase or a slight rim-like enhancement that persisted across the phases, while only 1 patient presented a nodular peripheral enhancement ($n=1$). Specifically, the most frequent radiologic pattern was a progressive central contrast uptake (from hypo-enhancement to isohyper-enhancement, *pattern-1*, Fig. 1) in 6 patients, followed by stable peripheral enhancement without changes through the phases (*pattern-2*, Fig. 2) and persistent minimal uptake through all phases (*pattern-3*, Fig. 3), 4 and 3 patients in each pattern, respectively (Table 2).

Table 2
Radiological features of the 13 patients with central revision.

HEHE[a] characteristics	
Multinodular disease n, (%)	7 (54)
Uninodular disease n, (%)	3 (23)
Confluent/diffuse n, (%)	3 (23)
Extrahepatic diseases n, (%)	4 (30.8)
Liver capsule retraction n, (%)	2 (15.4)
Lymph node involvement n, (%)	0
Macrovascular invasion n, (%)	0
Contrast-enhancement pattern	
T1-weighted sequences hypo-intensity (MRI)[b]	7/7
Baseline hypo-density (CT)[c]	6/6
Type 1 pattern	6/13
Type 2 pattern	4/13
Type 3 pattern	3/13

[a] HEHE: hepatic epitelioid hemangioendothelioma.
[b] MRI: Magnetic Resonance Imaging.
[c] CT: Computed Tomography*Pattern-1*: central progression (from hypo-to-isoto hyperenhancement); *Pattern-2*: stable peripheral without changes; *Pattern-3*: persistent minimal uptake through the phases.

3.4. Follow-up and treatment

During follow-up, 5 out of 13 patients underwent the same imaging modality as at baseline assessment, while the other 8 patients were evaluated alternatively by either CT or MR. After a median follow-up of 6.7 years (IQR; 4.3–12.9), 11 (44%) of the 24 patients developed at least one tumor progression and 7 (29.2%) had died. Seven (29.2%) patients did not receive any specific therapy, while 17 (70.8%) of them received at least one first-line treatment (Table 3): liver resection (LR, $n=7$, 29.2%), systemic treatments ($n=6$, 25%), and liver transplantation (LT, $n=4$, 16.7%). Four of the 7 patients treated with LR had unilobar involvement and 3 had multinodular disease. Only one of the resected patients had lung metastases but <1 cm and these have been stable for more than 5 years. Three patients were under yearly radiologic follow-up, two every 6 months while 2 patients did not receive a regular control. Four of the 7 resected patients developed tumor recurrence in the form of intrahepatic recurrence. Two of these patients received radiofrequency (RFA), one LT (5 years after LR) and one was just followed-up.

Of the 6 patients treated with systemic therapies, 4 (66%) had extrahepatic disease and 3 (50%) had radiological follow-up every 3 months while 3 patients were followed up every 6 months. One patient received interferon alpha (IFN-α) followed by paclitaxel/carboplatin, one IFN-α followed by paclitaxel alone, one paclitaxel alone as first-line and cisplatin/etoposide as second-line therapy, one interleukin-12 followed by IFN-α, one received IFN-α and liposomal doxorubicin and one IFN-α alone. None of them showed objective response at imaging, four (66%) developed radiologic tumor progression due to the growth of preexisting intrahepatic lesions and 2 of these patients developed symptoms at progression. In three patients, treatable progressions were approached with locoregional therapy (RFA or ethanol injection) and one with LR.

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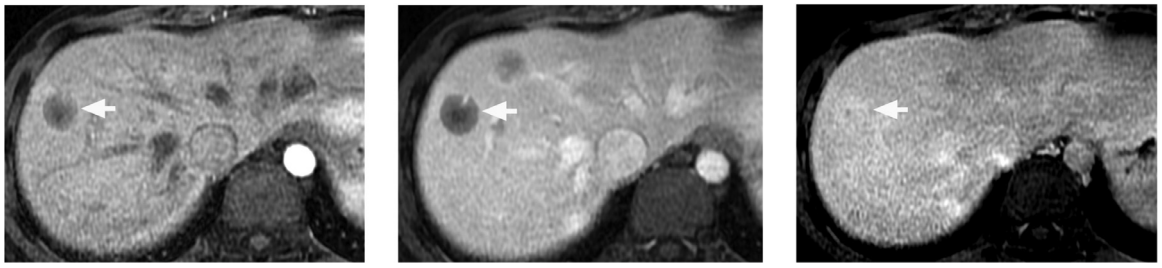

Fig. 1. Pattern of enhancement during the different phases of the dynamic study. Panels a, b and c correspond to arterial, portal venous and delayed venous phase, respectively, in a patient with a type 1 dynamic pattern characterized by central progression (from hypo to Isohyperenhancement arrows);

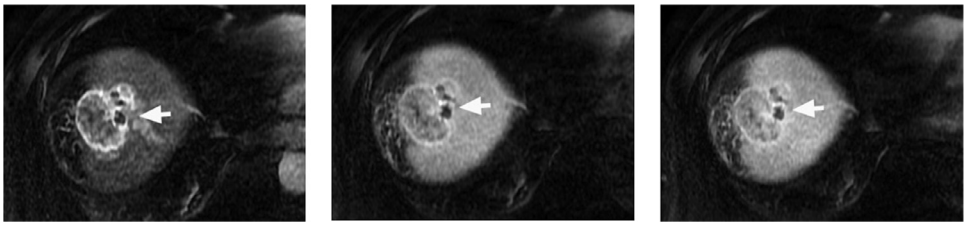

Fig. 2. Pattern of enhancement during the different phases of the dynamic study. Panels a, b and c correspond to arterial, portal venous and delayed venous phase, respectively, in a patient with a type 2 dynamic pattern characterized by a peripheral stable enhancement.

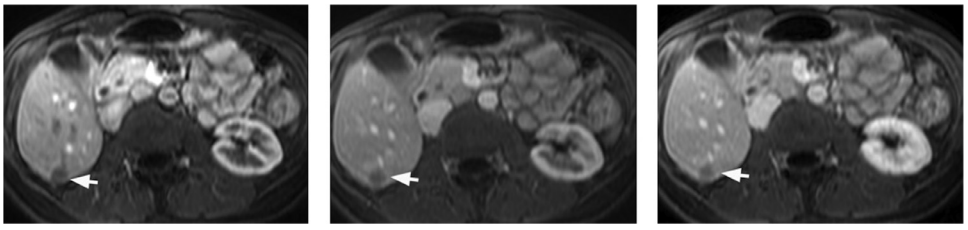

Fig. 3. Pattern of enhancement during the different phases of the dynamic study. Panels a, b and c correspond to arterial, portal venous and delayed venous phase, respectively, in a patients with a type 3 dynamic pattern characterized by minimal contrast uptake with a barely seen peripheral enhancement that remains unchanged during the different phases.

Table 3
Patient characteristics according to the first treatment received.

HEHE[a] characteristics	LR [b](n.7)	LT[c](n.4)	Systemic treatments (n.6)	No treatment (n.7)	All (n.24)
Bilobar disease n., (%)	3 (42.9%)	3 (75%)	4 (66.7%)	7 (100%)	17 (70.8)
Multinodular disease n., (%)	3 (42.9%)	3 (75%)	4 (66.7%)	6 (85.7%)	16 (66.7)
Extrahepatic disease n., (%)	1 (14.3%)	2 (50%)	4 (66.7%)	5 (71.4%)	12 (50)
Lymph nodes involvement n., (%)	1 (14.3%)	2 (50%)	0	0	3 (12.5)

[a] HEHE: hepatic epitelioid hemangioendothelioma.
[b] LR: Liver resection.
[c] LT: Liver transplantation.

Two of the 4 patients who were transplanted presented extrahepatic disease at the time of liver transplantation: one in the lung and one in the peritoneum, spleen and regional lymph nodes. One patient was radiologically followed-up every 3 months, one yearly while two patients were not under regular control. One of the transplanted patients developed tumor progression before LT for the growth of intrahepatic lesions but no recurrence was observed after a follow-up of 4.3, 7.4 16 and 19.7 years.

The 7 patients who did not receive any specific treatment had bilobar involvement, 6 had multinodular disease and 5 had lung metastasis. Two patients were followed up by radiology every two months, one every three months and four patients at an irregular interval. Two of them progressed due to growth of preexisting tumoral lesions but none of them were treated.

3.5. Survival analysis

Five- and 10-year OS rates in the whole cohort were 91.5% and 51.9% respectively. OS according to treatment groups was 100% and 80% in patients treated with LR, 100% and 66.7% in LT patients, 83.3% and 62.5% in those treated with chemotherapy and 83.3% and 41.7% in patients not receiving any specific treatment. No significant difference in terms of survival was detected among the uninodular, multinodular and confluent radiological presentation ($p = 0.1887$) nor among baseline median size of the largest target lesion ($p = 0.8119$) or the contrast enhancement patterns ($p = 0.1887$). Similarly, solid areas ($p = 0.6537$), the presence of spindling cells ($p = 0.3477$), Ki-67 expression ($p = 0.9168$) or intravascular growth ($p = 0.3470$) were not found to be significantly related to a difference in terms of OS.

4. Discussion

The very scarce and heterogeneous data regarding the factors associated to the development of rare vascular tumors such as HEHE, reflects the need to establish collaborative studies to identify the profile associated to a higher risk of HEHE. From 1968–1975 several publications suggested the association between HEHE

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and thorium and/or vinyl chloride. However, these factors have never been prospectively considered in the literature. The most common thorium mineral is monazite, and the countries in which monazite is mined include India, Malaysia, Vietnam, and Brazil as well as the Iberian massif in Europe. In addition, no strong recommendation regarding diagnosis, prognosis or therapy can currently be postulated in this malignant vascular tumor. Based on this scarcity of data we decided to perform this international study involving three centers between Brazil and Barcelona.

Thus, our study aims to identify the clinical and radiological issues which arise in the management of this tumor in order to establish an international network which can thereafter consolidate a prospective research registry.

Despite the limited number of patients, the novelty of this cohort is the availability of clinical and radiological information gathered during decades of follow-up. Indeed, this is the first international study with central radiological imaging revision in HEHE which has identified 3 radiological patterns according to the contrast enhanced profile techniques and characterized the evolution of patients according to the baseline profile. In the liver cancer field CT or MR are equally recommended for staging. Thus, despite of the fact that the patients included in this study were evaluated by both techniques, our findings about different imaging patterns should be considered a valuable clinical observation that needs to be validated in larger cohort of patients.

In this cohort, HEHE appeared in the majority of cases as subcapsular, multinodular, hypo-dense or hypo-intense lesions at CT and T1-weighted sequences at MR, respectively. Confluent or diffuse presentation was described only in a small number of patients (23%) and the most frequent pattern was the progressive central contrast uptake (46%). In this regard, the peripheral enhancement of diffuse lesions on the CT scan is proposed as being very suggestive of HEHE especially when accompanied by subcapsular location, capsule retraction and compensatory hypertrophy of the unaffected liver segments [2,6]. However, only two patients (2/24; 8.3%) in our cohort presented capsule retraction.

Regarding the clinical and pathological features of our cohort, the male to female ratio, age of presentation and rate of absence of liver diseases were similar to those reported in the literature [2,3].

Interestingly, in our cohort two out of ten (20%) patients had surgical specimens with positive MVI, namely in liver explants. Similarly, Lai Q. et al. [4]. described this finding in 12.8% of the patients at liver explant, but in more than 40% of the cases at imaging before liver transplantation. No case of radiological MVI was reported in our cohort. However, radiological data were not available for central revision in one of the two pathologically confirmed MVI, and in the other patient the imaging quality was suboptimal. However, the low concordance in MVI detection between radiology and pathology in HEHE series could also reside in the absence of a distinctive MVI radiological pattern thus reflecting the need of a boost in sharing data in this disease.

The diagnostic confirmation of HEHE is based on histology but the differential diagnosis is often a challenge especially with angiosarcoma [7–9], which shares the expression of vascular endothelial markers, but, as a high grade malignancy, presents more pronounced nuclear pleomorphism, atypia, and considerably higher mitotic activity [7,10,11]. In our cohort, one male patient had been diagnosed with HEHE by needle biopsy, but finally received the diagnosis of angiosarcoma on the liver explant. Due to the abundance of fibrotic tissue, misdiagnosis is also common with intrahepatic cholangiocarcinoma, sclerosing HCC or even fibrolamellar HCC expressing vascular markers on intra-tumoral sinusoids [7].

As previously mentioned, despite the size of the cohort, the strength of this study lies in its ability to identify the issues which arise when analyzing the outcome of HEHE according to the baseline tumor burden. However, the retrospective nature of the study and the small sample size, hamper any assumption related to the applicability of pathological findings as potential prognosis factors of HEHE outcome. Similarly, no interpretation regarding the radiological response can be drawn due to the heterogeneous imaging follow-up.

Table 3 reflects the key role of the baseline tumor burden at the time of indicating treatment and also as a confounding factor when the outcome of patients is compared. In our cohort only 1 patient was resected with extra-hepatic spread and all but 2 patients who received systemic treatment had extra-hepatic spread. Indeed, the outcome of liver resection could inaccurately be considered as being always better than that of systemic treatment if tumor burden and stage are not considered.

The previous comments are linked to the assumptions made regarding the chemo-resistant profile of this tumor to conventional chemotherapy [12]. There is no evidence to support one treatment over another because all the data come from the off-label use of immune-modulating and antineoplastic agents in only a few patients. In this regard, IFN-α [13–15] has been chosen for its immune- and anti-angiogenetic effect, while the use of different specific anti-VEGF (vascular endothelial growth factor) agents such as sorafenib [16,17], bevacizumab [18], lenalomide, thalidomide and others has been based on the expression of vascular markers on the tumor. Lakkis et al. [19] described the case of two patients treated with metronomic cyclophosphamide suggesting a slight efficacy and an acceptable safety profile although it is a challenge to establish to what extent it was due to treatment or to the slow tumor growth per se. The small number of cases, the absence of known pretreatment prognostic factors and the heterogeneity of systemic therapies (IFN-a, different chemotherapeutic agents etc.) hamper any inferential analysis. Indeed, all these confounding factors have an impact on the current information regarding OS in these patients and reflect the need of having multicenter studies focused on this orphan tumor.

The 5-year OS rate of patients with HEHE after primary radical treatment is reported to be between 54–75% [2,20] and in patients undergoing LT the 5-year OS rate was 64% according to the "United Network for Organ Sharing (UNOS)" database [21] and 80.8% according to the ELTR registry [4]. Interestingly, the minimally acceptable 5-year post transplant survival of 50% is widely achieved although whether the risk for the patient after LT is higher than offering an alternative approach or no treatment at all should always be considered [22]. This consideration is especially relevant in a disease that arises in young patients and frequently has a slow natural course with reported survival times ranging from 4 months to 10 years [3].

All these comments reveal the lack of a detailed knowledge of the molecular mechanisms involved in this tumor and the absence of accurate parameters to predict prognosis and decide when treatment is worthwhile. In this sense, it is important to stress that all these limitations result in a very confusing setting for patients and physicians. HEHE diagnosis affects the emotional and productive life of these patients and the absence of evidence-based treatment decisions further impairs these aspects. In addition, the treatment applied may be associated with major adverse events that decrease quality of life, or even lead to death. As a consequence, any decision may be followed by regrets and feelings of guilt.

In summary, this multicentric study reflects the heterogeneous profile of patients with HEHE and reveals the need to create an international network in order to study this tumor and better characterize these patients - mostly middle-aged females - who are currently orphan of evidence-based management.

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Disclosures

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Writing assistance

Diane Segarra.

Author contributions

Concept and design of the study: Vinicius Nunes, Jordi Bruix and Maria Reig; data collection: Vinicius Nunes, Marco Sanduzzi-Zamparelli, Carla Montironi and Jordi Rimola; statistical analysis: Victor Sapena; analysis of results and writing of article: Marco Sanduzzi Zamparelli, Jordi Rimola, Carla Montironi, Vinicius Nunes, Venancio Avancini Ferreira Alves, Víctor Sapena, Leonardo Gomes da Fonseca, Alejandro Forner, Flair José Carrilho, Alba Díaz, Carla Fuster, Joana Ferrer, Josep Fuster, Carmen Ayuso, Manel Solé, Jordi Bruix and Maria Reig. Final review and editing of the article: Jordi Bruix and Maria Reig. All authors approved the last version of the manuscript.

Declaration of Competing Interest

None.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2020.05.003.

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