



The challenging surgical management of hepatic epithelioid hemangioendothelioma: a narrative review

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Background and Objective: Hepatic epithelioid hemangioendothelioma (HEHE) is an uncommon vascular endothelial cell cancer involving the hepatic tissue with full malignant potential. HEHE diagnosis is challenging because blood tests and radiological findings are often non-pathognomonic. Therapeutic possibilities are manifold, ranging from a simple “wait and see” to surgical approaches, up to systemic therapies with vascular endothelial growth factor (VEGF) and mechanistic target of rapamycin (mTOR) inhibitors. The standardized adoption of the surgical approaches, namely resection or transplantation, still remains unclear. Aim of this review is to clarify the role of the surgical strategies for the management of HEHE.

Methods: A review of the literature was done with the intent to focus on the relevant studies exploring the role of the different surgical therapies. A search of these studies was done using the electronic database MEDLINE-PubMed.

Key Content and Findings: The surgical approaches, namely resection or transplantation, represent the best option in treating well-selected patients with HEHE. Resection is indicated in the case of single lesion or oligonodular monolobar disease. Liver transplantation is indicated in the case of multifocal bilobar disease, even in the presence of resectable extrahepatic disease. The potential role of a minimally invasive approach should represent a relevant field to explore.

Conclusions: The impact of surgery for the treatment of HEHE requires further studies to further clarify its relevant role. Standardized approaches are required.

Keywords: Hemangioendothelioma; liver transplantation (LT); mini-invasive; resection

Submitted Oct 12, 2021. Accepted for publication Aug 22, 2022.

doi: 10.21037/cco-21-139

View this article at: <https://dx.doi.org/10.21037/cco-21-139>

Introduction

Epithelioid hemangioendothelioma (EHE) is an uncommon vascular endothelial cell cancer composed of epithelioid and histiocyte-like vascular endothelial cells. EHE is now classified by the World Health Organization as a tumoral condition with the full potential of malignancy (1). EHE can occur in multiple body parts: soft tissue, neck, head, pleura, lungs, and bones. Hepatic EHE (HEHE) represents

an even less commonly observed cancer involving the liver, with 1–2 cases reported every 1 million people (2). HEHE is predominant in females (M:F ratio 2:3) and typically occurs between 30 and 50 years (3). HEHE can be single, multiple, or diffuse. In many cases, the tumor is multifocal at the time of diagnosis.

HEHE represents a low-to-medium grade cancer (4). The HEHE malignancy degree is between hemangioma

Table 1 The search strategy summary

Items	Specification
Date of search	13-05-2022
Databases and other sources searched	PubMed
Search terms used	(Liver OR hepatic) AND (hemangioendothelioma OR haemangioendothelioma OR HEHE)
Timeframe	2010–2022
Inclusion and exclusion criteria	Inclusion criteria: study type = original article; language = English
Selection process	Authors independently performing the selection: F Giovanardi and Q Lai

and hemangiosarcoma (5). In this tumor, epithelioid and dendritic-like cells infiltrate the hepatic sinuses (6). In a more advanced stage, hepatic/portal veins infiltration and distal metastases are often observed. Common sites of extrahepatic disease are bones, lymph nodes, spleen, lungs, and peritoneum (7). No specific clinical manifestations are present for this pathology (8). HEHE is very often initially misdiagnosed due to atypical clinical manifestations (3), being diagnosed typically only after pathological examination. Moreover, the HEHE radiological behavior is nonspecific. Differential diagnosis must be achieved from multifocal metastases, multifocal hepatocarcinoma, peripheral cholangiocarcinoma, abscess, or cavernous hemangioma. At second-level imaging, the main HEHE features are (I) the peripheral location of the lesions, (II) the merging aspect of the multifocal lesions, and (III) the capsule retraction (9,10).

However, capsule contraction has been observed only in lesions >2 cm (9). The etiology of HEHE is not fully clear. Different risk factors have been proposed, like the use of contraceptives, primary biliary cholangitis, alcoholic abuse, the presence of viral hepatitis, or the exposure to toxic substances like asbestos, polyurethane, chloroethylene, and silica (7). A specific genetic mutation, namely the translocation t(1/3)(P36/25), has been observed as a specific mutation in HEHE. However, it has not been fully elucidated how these fusion transcripts lead to tumorigenesis (11).

The most common signs and symptoms observed in HEHE patients are right upper abdominal pain (48.6%), hepatomegaly (20.4%), and anorexia (15.6%). Uncommonly, Kasabakh-Merritt syndrome and brucellosis have been described (12). Liver-specific blood tests and tumor markers are generally routine (3,13). We present the

following article in accordance with the Narrative Review reporting checklist (available at <https://cco.amegroups.com/article/view/10.21037/cco-21-139/rc>).

Methods

A review of the literature has been done with the intent to focus on the relevant studies exploring the diagnosis and surgical treatment of HEHE. Particular attention has been done on the role of the different surgical therapies. A search of these studies has been done using the electronic database MEDLINE-PubMed (*Table 1*). The identified studies are summarized on *Table 2*.

Diagnosis

The radiological diagnosis of HEHE is often challenging. Using magnetic resonance imaging (MRI), the most common radiological aspect of the tumor is observed in T2-weighted images, with peripherally distributed lesions with target appearance (34). Gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced MRI should also be functional (35). After positron emission tomography (PET), fluorodeoxyglucose (FDG) uptake was reported in only two-thirds of the HEHE cases (36).

Histopathology remains the best way to diagnose this tumor (37). Fine-needle aspiration or biopsy followed by immunohistochemical staining represent the best methods for the diagnosis (38). However, a false negative rate of 10% has been observed after the biopsy (39). Differential diagnosis must be made with focal nodular hyperplasia or hemangiosarcoma (40). At immunohistochemistry, positivity for CD31, CD34, or Factor VIII-related antigen are typical. Recently, an attempt to also identify a miRNA

Table 2 Summary of the currently available studies focused on the surgical management of HEHE

Author	Year	N	Diagnostic methods	Tumor size, mean, cm	Metastasis	Treatment	Recurrence rate, %	Survival, %
Thin <i>et al.</i> (14)	2010	1	Liver biopsy	NA	Intrahepatic metastasis	LT	0	100 (5-year)
Grotz <i>et al.</i> (15)	2010	22	Liver biopsy	NA	Lung, peritoneum, bone, brain and skin	LR or LT	40	62 (LR, 5-year), 46 (LT, 5-year)
Wang <i>et al.</i> (16)	2012	21	Surgical specimens	NA	Lung metastases, diaphragm/abdominal-wall metastases	LR, LR followed by TACE, or LT	NA	74 (LR, 3-year), 33 (LR followed by TACE, 3-year), 0 (LT, 3-year)
Thomas <i>et al.</i> (17)	2014	7	Liver biopsy, diagnostic laparoscopy, surgical specimens	3.6	Lung	Hepatectomy or LT	43	83 (5-year)
Theodosopoulos <i>et al.</i> (18)	2013	5	Liver biopsy	4	Intrahepatic metastasis	Surgical resection with a non-formal hepatectomy or wedge resection	40	60 (2-year)
Orlando <i>et al.</i> (19)	2013	108	Percutaneous needle, surgical, or combined biopsies	NA	Osseous and peritoneal localizations	LT	NA	72 (5-year)
Groeschl <i>et al.</i> (20)	2014	12	Liver biopsy, surgical specimens	NA	NA	Segmental resection, lobectomy/extended resection, LT	NA	57 (LR, 1-year), 80 (LT, 1-year)
Remiszewski <i>et al.</i> (21)	2014	10	Liver biopsy	5.1	Lymph node metastases	LT	0	90 (5-year)
Lin <i>et al.</i> (22)	2015	1	Surgical specimens	NA	No	LT	0	100 (5-year)
Sundar Alagusundaramoorthy <i>et al.</i> (23)	2015	11	Liver biopsy	NA	NA	LT	NA	79 (5-year)
Dong <i>et al.</i> (24)	2015	3	Liver biopsy	NA	NA	LR and RFA, or LT	0	100 (3-year)
Jung <i>et al.</i> (25)	2016	6	Liver biopsy	NA	NA	LR or LT	17	83 (5-year)
Abdoh <i>et al.</i> (26)	2016	1	Liver biopsy	NA	Intrahepatic metastasis	LT	100	0 (1-year)
Samuk <i>et al.</i> (27)	2016	1	Liver biopsy	NA	Lung	LT	0	100 (5-year)
Lai <i>et al.</i> (28)	2017	149	Percutaneous and/or surgical biopsy	NA	Lung, breast	LT and adjuvant therapy	25	81 (5-year)
Konstantinidis <i>et al.</i> (29)	2018	67	NA	14.8	NA	LR or LT	NA	83 (5-year)
Wang <i>et al.</i> (30)	2018	1	Liver biopsy	4.7	No	LR + chemotherapy	0	100 (15-year)

Table 2 (continued)

Table 2 (continued)

Author	Year	N	Diagnostic methods	Tumor size, mean, cm	Metastasis	Treatment	Recurrence rate, %	Survival, %
Noh <i>et al.</i> (31)	2020	19	Liver biopsy	3.5	NA	LR, LR + chemotherapy, LT + radiation therapy, LT + chemotherapy	NA	88 (5-year)
Sanduzzi-Zamparelli <i>et al.</i> (32)	2020	11	Surgical specimens, needle biopsy or “wedge-biopsy”	NA	Lung, lymph node metastases	LR or LT	36	100 (5-year)
Krasnodebski <i>et al.</i> (33)	2020	18	Liver biopsy	NA	Hilar lymph nodes	LT	0	41 (5-year)

HEHE, hepatic epithelioid hemangioendothelioma; N, number; %, percentage; NA, not available, LT, liver transplantation; LR, liver resection; TACE, trans-arterial chemoembolization.

expression spectrum has been made to improve the diagnostic ability (41).

Liver resection

Due to its rarity, HEHE does not represent a good target for randomized controlled trials with multiple treatment strategies. Currently, several therapeutical strategies are used to manage HEHE, namely hepatic resection and liver transplantation (LT), radiotherapy/chemotherapy, anti-angiogenic drugs, locoregional radiological therapies, and the observation-and-waiting approach (42).

Using hepatic resection *vs.* LT represents a topic of debate, with some controversies existing due to the challenging possibility to compare these two strategies in rare cancer.

Liver resection may be a curative strategy in well-selected cases in which the lesion is single or the disease is oligonodular and monolobar. However, the HEHE diagnosis is often made when an extensive involvement of the liver is reported (43). Therefore, radical hepatic resection should relate to relevant comorbidities, like post-resection liver failure. On the opposite, a conservative resection should not eradicate cancer, thus being connected with local recurrence or distant metastases (5).

Recently, the segmental hepatic resection approach has been implemented due to improved knowledge of intrahepatic anatomy. Segment-oriented resection consents to reach a radical strategy with a maximum of liver parenchyma preservation. This surgical approach looks to have great potential for a HEHE cure because this tumor typically raises in a liver without an underlying cirrhotic

disease. Therefore, this condition permits complex liver resections.

Both LT and hepatic resection should be considered successful strategies for obtaining reasonable long-term survival (39). However, the high rate of post-transplant mortality and morbidities observed, like infection (44,45) and graft failure (46), should be considered when the LT strategy is chosen. Moreover, more significant blood loss, prolonged operating procedures, and extended hospital stay are observed (47). In general, patients receiving LT have early (≤ 3 months) and late (> 3 months) mortality rates ranging 1–5% and 22% (28), respectively, which are higher than the mortality rates reported after hepatic resection (0–3%) (48).

Laparoscopic vs. open resection

The potential advantage of mini-invasive liver resection (MILS) for HEHE management has not been fully explored. However, such an approach should be a reasonable approach in the setting of this tumor.

HEHE is often observed in its multifocal form, with several lesions near the liver surface (49). Therefore, MILS with multiple partial resections should be a possible strategy to use in this case. MILS correlates with minor intraoperative blood loss, shorter length of hospital stay, and limited postsurgical adhesions (50). Moreover, MILS is suitable for newly managing intrahepatic recurrence. Also in this case, repeat MILS relates to less intraoperative blood loss and shorter hospital stay than open repeat resection (51,52). Therefore, repeat MILS should be considered a valuable

opportunity to treat potentially resectable recurrent HEHE.

The appropriate surgical margin to reach for the cure of HEHE has not been clearly stated. Some experiences reported that tumor cells should be observed within 1 cm from the principal lesion. However, no studies correlating between surgical margins <1 cm and recurrence have been reported (53). On the opposite, a negative surgical margin has been demonstrated to be sufficient in all liver sarcomas, including HEHE (29). Therefore, a 1-cm margin looks not to be necessary, but HEHE resection should only reach a negative margin of resection.

Liver transplantation

LT represents the best therapeutic option for unresectable HEHE, namely in the conditions in which the disease is multifocal and/or bilobar. However, to date, less than 300 procedures have been done, most of them being reported in three multicentre studies from Canada (N=11), the United States (N=110), and Europe (N=149) (28,54,55). To date patient selection criteria and an algorithm for the optimal management of HEHE are still missing. Therefore, the mindset of the LT community remains doubtful in managing this tumor.

So far, good outcomes have been reported. In the study from the United States (period: 1987–2005), the 5-year survival was 67% (54). The European study [1989–2017] (28) had 5- and 10-year survival percentages of 79.5% and 74.4%, respectively. Both studies demonstrated that the presence of the extrahepatic disease did not represent an absolute contraindication for LT.

The HEHE-LT score proposed by Lai *et al.* identified the presence of macrovascular involvement at pathology, the waiting time before transplantation shorter than four months, and hilar nodal metastases as three independent risk factors for HEHE recurrence after transplant (28).

Thus, considering these variables, three classes of post-LT recurrence risk have been identified, with a 5-year disease-free survival rate ranging from 93.9% in the low score group to 38.5% in the high score one ($P < 0.001$). The limit of the HEHE-LT score is that two out of three variables can be confirmed only after surgery.

Systemic treatments

Several chemotherapeutic drugs have been shown to be effective for the treatment of HEHE. Considering the vascular nature of this tumor and the presence of the

receptors for the vascular endothelial growth factor (VEGF) in HEHE cells, it is postulated that VEGF plays a role in the growth of this cancer. In combination with a cell cycle inhibitor (i.e., sorafenib, pazopanib, bevacizumab), VEGF inhibitors (i.e., capecitabine), consented to achieve sound curative effects. For patients treated with pazopanib, the change in tumor density after computed tomography (CT) without evident tumor contraction or calcification can be considered a strong indication of tumor response (56). In patients with metastatic disease, adjuvant chemotherapy should represent an effective alternative therapy to prevent tumor recurrence.

Other drugs have been adopted for curing HEHE, like mTOR inhibitors, thalidomide, pegylated liposomal doxorubicin, and metronomic cyclophosphamide, interferon-alpha, and 5-fluorouracil (57,58). A randomized multicenter study from China showed that the Huaier granule could reduce the risk of postoperative HEHE recurrence (6). Huaier granule, a water-based product of Huaier extract, has an anti-tumor response thanks to the inhibition of tumor angiogenesis and the induction of the cell-cycle arrest at the G0/G1 checkpoint (59). Huaier granule also regulates innate immunity by stimulating cytokine release and production of reactive oxygen species (60).

More studies based on more extensive databases are needed to provide guidelines for HEHE diagnosis and treatment.

Discussion

Because of its rarity, no standardized flowchart for the treatment of HEHE exists. Only recently, a flow chart for the management of HEHE patients undergoing LT has been proposed, but not yet prospectively validated (*Figure 1*) (28). In a large review collecting 253 HEHE patients, the reported 1-, 3-, and 5-year overall survival rates were 83.4%, 55.7%, and 41.1%, respectively (3). Among the different kinds of treatments proposed, hepatectomy was the most frequently chosen, followed by LT, chemotherapy, radiotherapy, locoregional therapies, and observational follow-up. Hepatic resection consented to reach the best 5-year survival (i.e., 75%) (61). However, this therapy is often not indicated because the tumor is multifocal at the diagnosis.

The clinical course of HEHE is hugely variegated, passing from complete spontaneous regression to aggressive rapid progression. This heterogeneity in the observed results is principally connected with the significant

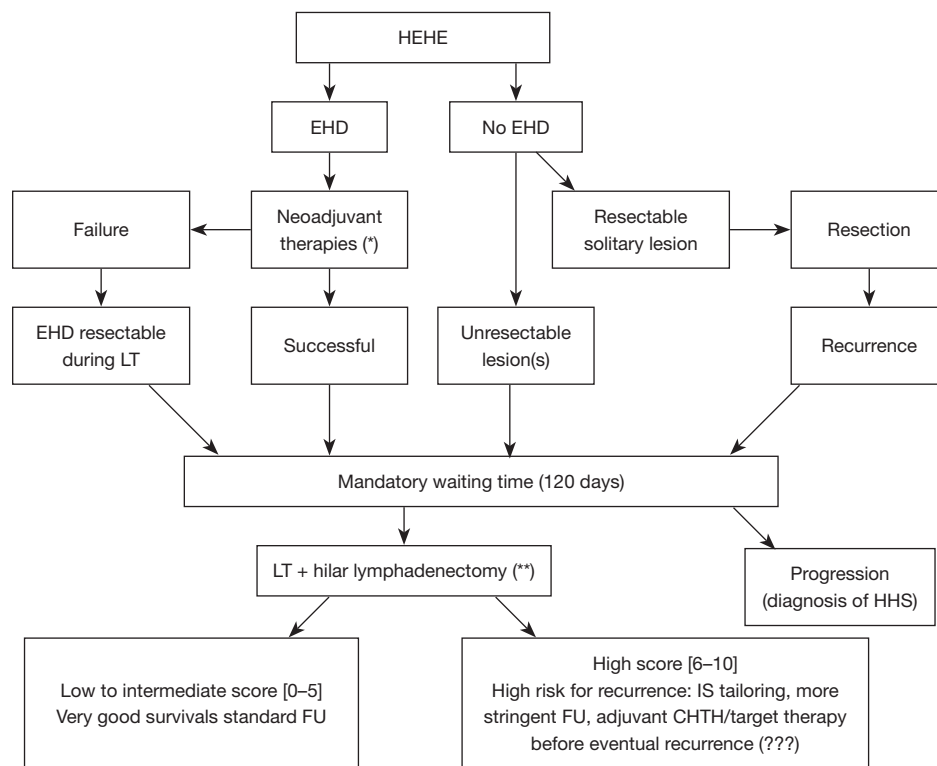


Figure 1 HEHE therapeutic algorithm proposed by Lai et al. (28) for the management of patients with LT: with modifications. (*) no standardized neoadjuvant approach; (**) histological examination combining immunohistochemistry and H&E staining. EHD, extrahepatic disease; FU, follow-up; HEHE, hepatic epithelioid hemangioendothelioma; HHS, hepatic hemangiosarcoma; IS, immunosuppression; LT, liver transplantation; CHTH, chemotherapy.

differences observed in the initial tumor characteristics of patients treated with surgical *vs.* non-surgical approaches.

For example, in the two Surveillance, Epidemiology, and End Results (SEER) studies published on HEHE, significant differences have been reported in terms of survival. In the first study (N=56, period 1973–2014), 1-year overall survival rates were 57% *vs.* 67% *vs.* 80% in patients undergoing resection, no surgical approaches, and LT, respectively (31). The more recent analysis (N=79, period 2004–2016) reported 1- and 5-year overall survival of 87% *vs.* 75% and 61% *vs.* 37% in the surgical *vs.* the non-surgical group, respectively (62).

Several surgical approaches, like hepatic artery ligation, hepatic resection, or LT, have been utilized to cure HEHE (Table 2) (14-28,30,32,33,50,63). Hepatectomy is adopted to cure localized single lesions, whilst LT represents the treatment of choice to treat multifocal diseases (51). In a retrospective study on 30 HEHE patients treated at the Mayo Clinic, most patients undergoing surgery had no extrahepatic involvement at the time of surgery. However,

overall survival was not inferior in patients with extrahepatic involvement, arguing that metastatic disease may not be considered an absolute contraindication for surgery (46). This observation was also confirmed in the setting of LT (28). In detail, 40 patients transplanted with the extrahepatic disease had 5-year survivals of 72%, a remarkable survival rate in patients with metastases at the time of transplant (28).

Conclusions

HEHE is rare cancer for which different treatment strategies have been applied. Surgery often represents the first choice in terms of obtainable results. LT is indicated in multifocal and/or bilobar disease, while liver resection is indicated only in the less common condition of single or oligonodular monolobar disease. The minimally invasive surgical approach has shown comparable results to open surgery in terms of survival. Further studies are needed to establish the safety and reproducibility of minimally invasive surgery in treating this type of cancer. VEGF inhibitors,

often in combination with other chemotherapeutic drugs, can be used for patients exceeding the surgical criteria.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Giovanni Levi Sandri) for the series "Hepatobiliary and Pancreatic Cancers: An Update of Surgical Treatments" published in *Chinese Clinical Oncology*. The article has undergone external peer review.

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at <https://cco.amegroups.com/article/view/10.21037/cco-21-139/rc>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://cco.amegroups.com/article/view/10.21037/cco-21-139/coif>). The series "Hepatobiliary and Pancreatic Cancers: An Update of Surgical Treatments" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Giovanardi F, Larghi Laureiro Z, Meo GA, Hassan R, Lai Q. The challenging surgical management of hepatic epithelioid hemangioendothelioma: a narrative review. *Chin Clin Oncol* 2022;11(4):27. doi: 10.21037/cco-21-139