

# Outcomes of hepatic epithelioid hemangioendothelioma with different managements: a retrospective investigation

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**Abstract. – OBJECTIVE:** Hepatic epithelioid hemangioendothelioma (HEH) is an extremely rare tumor, and no standard treatment has been established yet. This study aimed to retrospectively investigate the outcomes of different managements for HEH patients.

**PATIENTS AND METHODS:** From March 2014 to November 2019, a retrospective investigation was performed among 50 HEH patients to summarize the outcomes of different managements. Their medical records were collected, and the outcome of each management was evaluated based on radiological images.

**RESULTS:** Of the 50 HEH patients examined, 80% were asymptomatic, and 94% had multiple intrahepatic lesions. Extrahepatic metastases were detected in 54% of patients, and 82% of patients were radiologically misdiagnosed. 16 (88.9%) of 18 patients with initial observation had progressive disease (PD). Of 12 patients with curatively intended surgery or radiofrequency ablation (RF), 10 (83.3%) of them had a recurrence. Six treated patients with interferon- $\alpha$  had results of 4 partial responses (PR), 1 complete response (CR), and 1 stable disease (SD). Of 6 patients with thalidomide, 4 patients had PD, and 2 patients had SD. Four patients treated with chemotherapy had 3 PD and 1 SD. Five patients treated with targeted therapy had 2 PR, 2 PD, and 1 SD.

**CONCLUSIONS:** During our observation, we found that HEH patients had a high chance of PD. The risk of recurrence after surgery or RF was high. The encouraging result of interferon- $\alpha$  therapy makes it a promising treatment for HEH.

*Key Words:*

Liver cancer, Epithelioid hemangioendothelioma, Interferon, Surgery, Radiofrequency ablation.

## Introduction

Epithelioid hemangioendothelioma (EH), was firstly described by Weiss and Enzinger in 1982, is an extremely rare tumor, and the clinical

course is unpredictable<sup>1,2</sup>. Multiple organs could be involved, such as liver, lung, spleen, and heart. Surgical resection, liver transplantation, chemotherapy, targeted therapy, and immunotherapy have all been used in the treatment of hepatic epithelioid hemangioendothelioma (HEH) patients. Several studies<sup>3-7</sup> reported that liver transplantation achieved a long-term satisfying result, even for patients with extrahepatic metastases. However, the shortage of organ donation limits the accessibility of liver transplantation for most HEH patients unless they are in critical condition. Treatment with anti-angiogenesis drugs, chemotherapy, transarterial embolization (TAE) or targeted therapy have all been reported with different results<sup>8-11</sup>. Moreover, due to the extremely low incidence of HEH, a prospective clinical trial is very hard to conduct. At present, no standard treatment has been established yet. So, investigating and summarizing effective medicine or management would be conducive to direct prospective clinical trials. This study was aimed to retrospectively investigate the outcomes of different managements for HEH patients, which could provide valid information for future clinical trials.

## Patients and Methods

### *Patients Eligibility*

From March 2014 to November 2019, a retrospective investigation was performed among a group of HEH patients to summarize the clinical characteristics and outcomes of different managements. Patients with HEH were contacted privately and investigated with the following criteria: 1) patients aged  $\geq 18$  years with histologically confirmed HEH; 2) patients with the willingness to accept the investigation; 3) detailed medical records could be provided, including records of each treatment, lab test and radiological images

before and after each treatment; 4) patients should have regular follow-up including computed tomography (CT) or magnetic resonance imaging (MRI). Exclusion criteria: 1) EH of other sites instead of the liver; 2) medical records or radiological images were not complete enough to analyze the outcome of the treatment. A consent form to use their clinical data for medical research was signed by each of them.

### **Methods**

Patients' medical records were reviewed retrospectively, and the collected data included the following: demographics, symptoms, ways of pathological diagnosis, distal metastasis, treatment, results of lab tests, and radiological images. Patients' performance status (PS) was assessed according to the Eastern Cooperative Oncology Group (ECOG). To analyze the outcome of observation, all patients with the initial intention of observation instead of any treatment after diagnosis were included. The definition of disease progression was made based on the comparison of radiological images (CT or MRI) during the observation period according to the Response Evaluation Criteria in Solid Tumors Committee (RECIST) criteria<sup>12</sup>. For patients with curatively intended surgery or radiofrequency ablation (RF), radiological images (CT or MRI) during the follow-up period were evaluated to detect the recurrence. For patients with medical treatment such as chemotherapy, targeted therapy, interferon- $\alpha$  or thalidomide, the effect of each treatment was assessed based on the radiological change during the treatment process according to RECIST criteria. Adverse events were assessed based on the medical records and the results of lab tests according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. For patients with the treatment of TAE, the effect was assessed based on radiological changes after the procedure according to RECIST criteria. For patients with non-simultaneous multi-managements, outcome analysis of each management was carried out respectively. The study was approved by the Institutional Ethical Review Board of the China-Japan Friendship Hospital.

### **Statistical Analysis**

Statistical comparison is not applicable due to the limited number of patients and diversified treatment strategies. Categorical variables are expressed as the number of cases, and continuous variables with normal distributions are expressed

as the means  $\pm$  standard deviation. Continuous variables with abnormal distributions are expressed as medians  $\pm$  inter-quartile range.

## **Results**

### **Demographics and Clinical Characteristics**

A total of 64 HEH patients were contacted privately, and 58 of them would like to accept the investigation. While 8 patients were excluded for incomplete medical records, and 50 HEH patients were finally included.

For all the 50 HEH patients, the median age at diagnosis was 36 years old (range: 21-61 years old), and the ratio of the male was a little higher than the female (54% vs. 46%). HEH was detected in 40 (80%) patients at the routine examination with no symptom. Only 2 (4%) patients had mildly affected PS (ECOG 1), and the rest 48 (96%) patients had normal PS (ECOG 0). Histological diagnosis was made by percutaneous liver biopsy in 38 (76%) patients and by surgical resection or biopsy in 12 (24%) patients. The median time between diagnosis and the investigation was 16.5 months. At the time of investigation, 7 patients were just diagnosed without a decision on the next step, and they were not included in any analysis of outcomes.

Before histological diagnosis, all patients had contrast-enhanced radiology. The results showed 47 (94%) patients had multiple intrahepatic lesions, and only 3 (6%) patients had a singular lesion. Extrahepatic metastases were detected in 27 (54%) patients, and most of them were in the lung. Three patients had multiple sites metastases (1 with lung + peritoneum, 1 with lung + spleen, and 1 with lung + bone). Radiological misdiagnosis was observed in 41 (82%) patients (Table I). Abnormality in serum tumor marker or liver function was rare ([Supplementary Table I](#)).

### **Management and Outcomes**

#### **Observation**

After histological diagnosis, 18 patients (9 male and 9 female; median age 36 with a range 22-53 years old) chose the observation with the routine examination. The median duration of observation was 15.5 months (range 5-58 months). Sixteen (88.9%) of them had progressive disease (PD), and only 2 (11.1%) patients had stable dis-

**Table I.** Radiological characteristics of HEH patients.

Variables	HEH patients, No. (%)
Number of patients	50
Radiology before diagnosis	
CE-CT+CE-MRI	29 (58%)
CE-CT alone	12 (24%)
CE-MRI alone	9 (18%)
Number of intrahepatic lesions	
Singular	3 (6%)
Multiple	47 (94%)
Metastasis	
None	23 (46%)
Lung alone	24 (48%)
Lung + other sites	3 (6%)
Radiological misdiagnosis	41 (82%)
Hepatic metastatic carcinoma	33 (66%)
Intrahepatic cholangiocarcinoma	2 (4%)
Angiosarcoma	2 (4%)
Granuloma	2 (4%)
Hemangioma	1 (2%)
Hepatocellular carcinoma	1 (2%)

HEH, hepatic epithelioid hemangioendothelioma; CE-CT, contrast enhanced computed tomography; CE-MRI, contrast enhanced magnetic resonance imaging

ease (SD) with observation time of 22 months and 36 months, respectively. The radiological changes of 18 HEH patients with initial observation were shown in [Supplementary Figure 1](#).

### **Surgery, RF, and TAE**

Curatively intended surgery or RF was performed in 12 patients (6 male and 6 female; median age 42 with a range of 21-56 years old), including surgery in 7 patients and RF in 5 patients (Table II). Another 5 patients accepted surgery, but the only biopsy was performed, which were not included in the analysis. After surgery or RF, no adjuvant therapy was used for all 12 patients. Ten patients (83.3%) had a recurrence, and the median time of disease-free was 4 months with a range of 3-34 months (Figure 1). Two patients had no recurrence with a follow-up period of 4 months and 19 months, respectively. Two patients with TAE were defined as PD at 4 months and 5 months after the procedure, respectively.

### **Interferon- $\alpha$ and Thalidomide**

Six patients had the treatment of interferon- $\alpha$  (4 male and 2 female, age range 22-36 years old). The range of duration with interferon- $\alpha$  was 12-24 months, and the results showed 4 with partial response (PR), 1 with complete response (CR), and

1 with SD. Only mild adverse event was recorded for all 6 patients (Table III). Six patients had the treatment of thalidomide (4 male and 2 female, age range 32-61 years old). The range of duration with thalidomide was 12-48 months, and the results showed 4 with PD and 2 with SD. Four patients had grade II paresthesia, and 1 patient had grade II constipation. Both female patients had menolipsis after the treatment of thalidomide (Table III). The radiological changes after the treatment of interferon- $\alpha$  or thalidomide were showed in [Supplementary Figure 2](#).

### **Chemotherapy and Targeted Therapy**

Four patients (3 female and one male, age range 22-34 years old) had the treatment of chemotherapy. Severe adverse events were recorded for 3 patients. Three of them had PD and 1 had SD. One patient with PD chose targeted therapy after the failure of chemotherapy. The detailed chemotherapy regime was listed in Table IV. Five patients (3 male and 2 female, age range 22-38 years old) had the treatment of targeted therapy, including apatinib for 3 patients, sunitinib for 1 patient, and bevacizumab + lenvatinib for 1 patient. Moderate adverse events were recorded for 2 patients with apatinib (hypertension grade II and urine protein/occult blood grade II). For 3 patients with apatinib, 2 had PR, and one had PD. The patient with sunitinib had SD. The patient with 8 cycles of pembrolizumab and 8 cycles of pembrolizumab + bevacizumab + lenvatinib was defined as PD (Table IV). The radiological changes for patients with chemotherapy and targeted therapy were shown in [Supplementary Figure 3](#).

### **Follow-up**

Two patients died during the follow-up with survival time of 16 months and 26 months, respectively. The rest 48 patients are alive and under regular follow-up with the radiological examination. A brief summary of outcomes of different managements was illustrated in Figure 2.

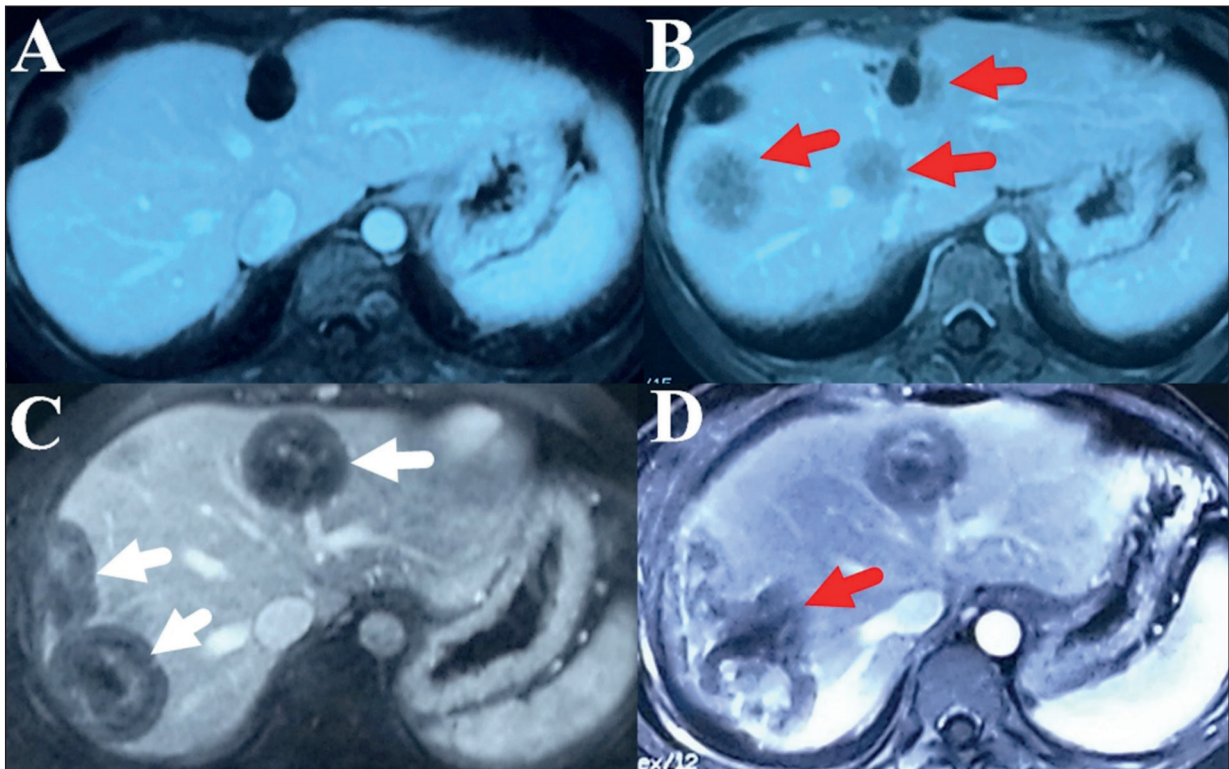
## **Discussion**

HEH is a very rare tumor, and the tumor's biological behavior is unpredictable. For most patients, the tumor was detected occasionally with no symptom. Due to the rarity and multicentricity of the disease, many patients were misdiagnosed as hepatic metastatic carcinoma. Although several studies have reported the radiological char-

**Table II.** Information of HEH patients with curatively intended surgery or radiofrequency ablation.

Patient number	Gender	Age (years)	Procedure	Adjuvant therapy	Outcome	Length of disease-free (months)
1	Male	21	Local resection of four lesions in segment VIII/VII/VI/IV	None	Recurrence	20
2	Male	48	Resection of left lateral lobe and local resection of one lesion in segment VI	None	Recurrence	4
3	Male	33	Resection of left lateral lobe and local resection of two lesions in segment VI/VII	None	Recurrence	3
4	Male	32	Resection of segment V/VI and local resection of three lesions in segment VII/IV/III	None	Recurrence	3
5	Female	44	Right hemihepatectomy and local resection of one lesion in segment IV	None	No recurrence	4
6	Male	27	Local resection of the single lesion in segment VIII	None	No recurrence	19
7	Female	55	Local resection of five lesions in segment VIII/VII/VI/V/IV	None	Recurrence	34
8	Female	32	Radiofrequency Ablation	None	Recurrence	3
9	Female	54	Radiofrequency Ablation	None	Recurrence	3
10	Female	42	Radiofrequency Ablation	None	Recurrence	26
11	Male	43	Radiofrequency Ablation	None	Recurrence	6
12	Female	56	Radiofrequency Ablation	None	Recurrence	4

HEH, hepatic epithelioid hemangioendothelioma.



**Figure 1.** **A** and **B**, A 21-year-old male HEH patient with surgical resection. **A**, No recurrence was detected at 6 months after surgery. **B**, Multi metastases were found at 20 months after surgery (marked by *red arrows*). **C** and **D**, A 32-year-old HEH female with radiofrequency ablation (RF). **C**, Three lesions were ablated by RF (marked by *white arrows*). **D**, Tumor progressed at 3 months after RF (marked by *red arrow*).

acteristics of HEH<sup>13-16</sup>, histological examination seems the only method for final confirmation. In this study, 82% of patients were misdiagnosed by contrast-enhanced CT or MRI.

Liver transplantation has been reported with satisfying long-term results<sup>7,17,18</sup>. However, due to the shortage of organ donors, liver transplantation is only accessible for HEH patients in critical conditions. A surgical resection is also a treatment option, but the long-term results are not well. In a retrospective single-center study, 3 out of 6 patients who underwent hepatic resection had disease relapse<sup>19</sup>. For most HEH patients, curative resection is implausible because of the multicentricity of the lesions. Palliative resection is not suggested since the tumor tends to behave aggressively after surgical resection<sup>20,21</sup>. In this study, 7 patients accepted curatively intended surgery, and 5 of them had a recurrence. Three patients recurred in a very short time. Patients with RF showed similar results. Four out of 5 patients recurred within 6 months after RF. The aggressive behavior after resection or RF may be caused by

the up-regulated hepatic growth factors, which makes both liver resection and RF cautious treatment options for HEH patients.

As HEH may keep stable or progress slowly, observation was suggested by some researchers<sup>22</sup>. In this study, 18 patients initially chose observation after diagnosis, and 88.9% of them had PD with a median time of 15.5 months. The result of our study didn't support the management of observation. Currently, no standard systematic therapy has been established for HEH patients. Chemotherapy, targeted therapy, and immunotherapy have all been used; however, the results were indeterminate<sup>23-26</sup>. Sorafenib has been reported to be effective, but most of them are case reports<sup>26,27</sup>. In a phase-2 study on sorafenib in EH patients, the response rate (PR+CR) was very low (2 out of 15 EH patients), and the study included EH patients with liver, lung, and bone<sup>25</sup>. In this study, 3 patients had apatinib, and 2 of them had PR, which indicated the potential value of apatinib in the treatment of HEH. Several cytotoxic chemotherapy regimens, including adriamycin,

**Table III.** Information of HEH patients with treatment of interferon- $\alpha$  and thalidomide.

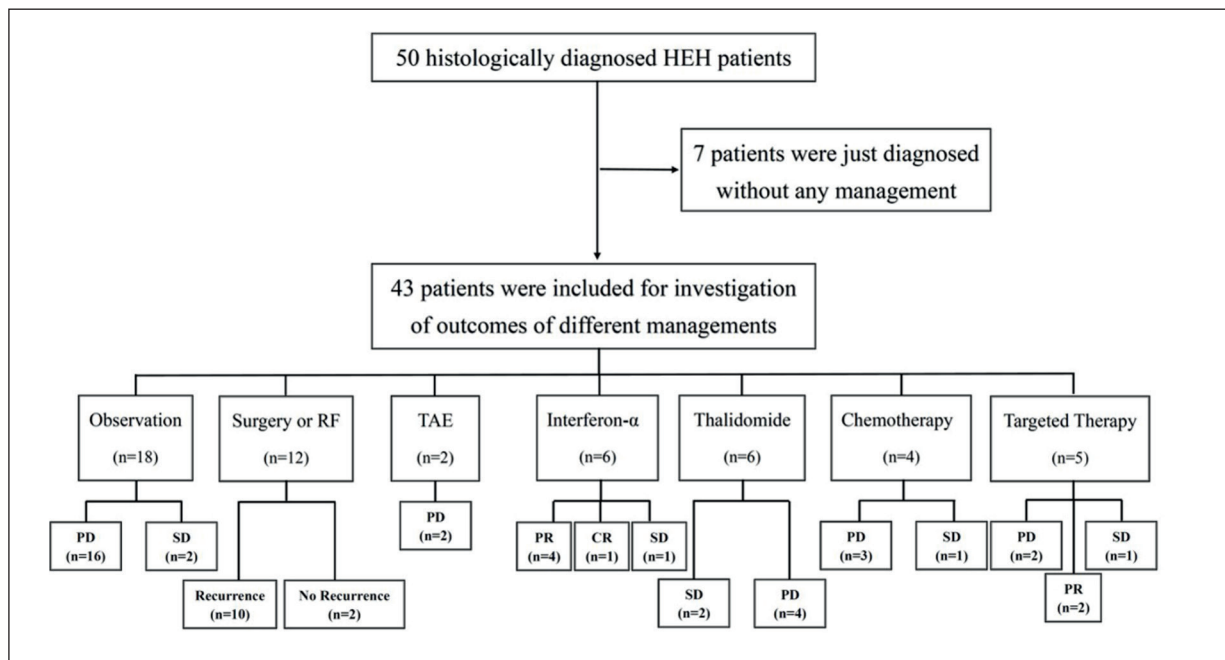
Patient number	Gender	Age (years)	Treatment	Length (months)	Effect	Adverse events
1	Male	31	Interferon- $\alpha$ 2b 3000000 IU iH qod	15	PR	Fever Grade I/Fatigue Grade I
2	Male	22	Interferon- $\alpha$ 1b 5000000 IU iH qod	12	PR	Fever Grade I
3	Female	27	Interferon- $\alpha$ 2b 3000000 IU iH qod	16	SD	Fever Grade I/Fatigue Grade I
4	Female	36	Interferon- $\alpha$ 2b 3000000 IU iH qod	18	CR	Fever Grade I/Fatigue Grade I/Alopecia Grade I
5	Male	24	Interferon- $\alpha$ 2b 3000000 IU iH qod	24	PR	None
6	Male	36	Interferon- $\alpha$ 2b 3000000 IU iH qod	18	PR	Fever Grade I
7	Female	41	Thalidomide 100 mg/d	12	PD	Constipation Grade II/Menolipsis
8	Male	48	Thalidomide 100 mg/d	12	PD	Constipation Grade I
9	Male	61	Thalidomide 150 mg/d	23	SD	Paresthesia Grade II
10	Male	32	Thalidomide 150 mg/d	18	PD	Paresthesia Grade II
11	Female	41	Thalidomide 100 mg/d	48	PD	Paresthesia Grade II/Menolipsis
12	Male	46	Thalidomide 150 mg/d	10	SD	Paresthesia Grade II

HEH, hepatic epithelioid hemangioendothelioma.

**Table IV.** Information of HEH patients with treatment of chemotherapy and targeted therapy.

Patient number	Gender	Age (years)	Regime/medicine	Cycles/length	Effect	Adverse events
1	Female	34	FOLFOX	3 cycles	SD	Emesis Grade III/Leukopenia Grade II
2	Male	22	FOLFOX + Gemcitabine	2 cycles	PD	Emesis Grade II/Leukopenia Grade II
3	Female	28	Paclitaxel + Endostatin	7 cycles	PD	Emesis Grade III/Leukopenia Grade II/Alopecia Grade II
4	Female	29	Bevacizumab + Docetaxel + Cisplatin	4 cycles	PD	Emesis Grade III/Leukopenia Grade II
			Apatinib	22 months	PR	Hand-Foot Syndrome Grade I/Diarrhea Grade I
5	Male	30	Apatinib	5 months	PD	Hypertension Grade II
6	Female	38	Apatinib	14 months	PR	Hand-Foot Syndrome Grade I/Hypertension Grade II/ Urine Protein and Occult Blood Grade II
7	Male	22	Sunitinib	9 months	SD	Diarrhea Grade I/Leukopenia Grade I/ Thrombocytopenia Grade I
8	Male	38	Pembrolizumab	8 cycles	PD	Leukopenia Grade I/Hypothyroidism
			Pembrolizumab + Bevacizumab + Lenvatinib	8 cycles		

HEH, hepatic epithelioid hemangioendothelioma; PR, partial response; SD, stable disease; CR, complete response; PD, progressive disease.



**Figure 2.** Brief summary of outcomes of HEH patients with different managements.

dacarbazine, and paclitaxel, have been reported effective for EH patients, but none of them were specific for HEH patients<sup>28-30</sup>. In this study, 4 patients had diversified chemotherapy regimens, while all of them had PD with moderate to severe adverse events. Considering the slow progression of HEH and side effects of chemotherapy, chemotherapy should be cautiously carried out unless further valid evidence is provided.

Due to the vascular origin of EH, thalidomide as anti-angiogenic therapy was intuitively proposed for the treatment of EH. Several case reports have showed that thalidomide could control the progression of EH<sup>8,31-34</sup>. In this study, 2 of 6 patients with thalidomide had SD, but no PR or CR was achieved. Interferon- $\alpha$  therapy for EH has also been proposed for tumor reduction and metastasis prevention<sup>9,35-37</sup>. Interferon- $\alpha$  has been reported to have cancer cell growth inhibition, activation of immune cells, inhibition of vascularization, and induction of cytokines<sup>38,39</sup>. However, the clinical effect of interferon- $\alpha$  for HEH patients has never been fully investigated. In this study, 6 patients with interferon- $\alpha$  had an encouraging result of 4 PR, 1 CR, and 1 SD. Although the satisfying results of 6 patients with interferon- $\alpha$  cannot guarantee the same effect on a larger group, it does provide a promising option and direct future

clinical trials. Although this is a retrospective study, due to the extreme rarity of the disease, the results still provide valuable clinical information for future research.

## Conclusions

Briefly, most HEH patients were asymptomatic and misdiagnosed as hepatic metastatic carcinoma. During observation, most HEH patients had progression. The risk of recurrence after curatively intended surgery or RF was very high. The encouraging result of interferon- $\alpha$  therapy makes it a promising option for HEH patients, but further clinical trials are needed.

## Conflict of Interest

The Authors declare that they have no conflict of interests.

## Acknowledgements

The authors want to thank all of the patients and their families for assisting in the implementation of this study.

## Funding

This study did not receive any funding.

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