

Outcomes of Hepatic Epithelioid Hemangioendothelioma with Different Managements: Retrospective Investigation of 50 Patients

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Outcomes of hepatic epithelioid hemangioendothelioma with different managements: Retrospective investigation of 50 patients

Running title: Outcomes of HEHE with different managements

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List of abbreviation: EH, epithelioid hemangioendothelioma; HEHE, hepatic epithelioid hemangioendothelioma; TAE, transarterial embolization; CT, computed tomography; MRI, magnetic resonance imaging; ECOG, Eastern Cooperative Oncology Group; RECIST, Response Evaluation Criteria in Solid Tumors Committee; SD, standard deviation; PD, progressive disease; SD, stable disease; PR, partial response; CR, complete response

Key words: liver cancer, epithelioid hemangioendothelioma, interferon

Novelty and Impact

Hepatic epithelioid hemangioendothelioma (HEHE) is a rare tumor and no standard treatment has been established. HEHE patients had a high chance of progressive disease during observation. The risk of recurrence after surgery or radiofrequency ablation was high. Treatment of interferon- α achieved partial and complete response for HEHE patients. The encouraging result of interferon- α makes it a promising treatment for HEHE.

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Abstract

Background: Hepatic epithelioid hemangioendothelioma (HEHE) is a rare tumor and no standard treatment has been established. This study was aimed to retrospectively investigate the outcomes of different managements for HEHE patients

Methods: From March 2017 to November 2019, a retrospective investigation was performed among 50 HEHE 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: For all the 50 HEHE patients, 80% were asymptomatic and 94% had multiple intrahepatic lesions. Extrahepatic metastases were detected in 54% patients and 82% patients were radiologically misdiagnosed. For 18 patients with initial observation, 16 (88.9%) of them had progressive disease (PD). For 12 patients with curative intent surgery or radiofrequency ablation (RF), 10 (83.3%) of them had recurrence. Six patients with interferon- α had results of 4 partial response (PR), one complete response (CR) and one stable disease (SD). For 6 patients with thalidomide, 4 patients had PD and 2 patients had SD. Four patients with chemotherapy had 3 PD and one SD. Five patients with targeted therapy had 2 PR (both with apatinib), 2 PD and one SD.

Conclusions: HEHE patients had a high chance of PD during observation. The risk of recurrence after surgery or RF was high. Interferon- α and apatinib were the managements with tumor response (PR or CR). The encouraging result of interferon- α makes it a promising treatment for HEHE.

Introduction

Epithelioid hemangioendothelioma (EH) is a rare tumor (estimated incidence of less than one in 1,000,000 worldwide) with a clinical course intermediate between benign hemangioma and angiosarcoma^[1]. EH was initially described in 1982 by Weiss and Enzinger^[2] and it can involve both soft tissues and visceral organs, including liver, lung, spleen and heart. Hepatic epithelioid hemangioendothelioma (HEHE) is a kind of clinical form of the disease. Due to the low incidence which makes randomized controlled trial implausible, no standard treatment has been established yet. Surgical resection, liver transplantation, chemotherapy, targeted therapy, and immunotherapy have all been used in the treatment of patients with HEHE. Several studies reported that HEHE patients who accepted liver transplantation had a well long-term survival, even with a known extrahepatic disease^[3-7]. However, due to the contradiction between the shortage of organ donation and numerous patients in the waiting list, liver transplantation seems to be inaccessible for most HEHE patients, unless they are in critical condition. So, identifying the effective medicine or management would benefit most of HEHE patients.

The rarity of HEHE combined with the common misdiagnosis has resulted in a variety of treatment strategies ranging from observation to chemotherapy. Treatment with anti-angiogenesis drugs, systemic chemotherapy, transarterial embolization (TAE), targeted therapy or combined therapies have all been utilized with varying results^[8-11]. This study was aimed to retrospectively investigate the outcomes of different managements for HEHE patients, which can provide valid information for

future clinical trial.

Patients and Methods

Patients eligibility

From March 2017 to November 2019, a retrospective investigation was performed among a group of HEHE patients to summarize the clinical characteristics and outcomes of different managements. Patients with HEHE were contacted and investigated with following criteria: 1) patients aged ≥ 18 years with histologically confirmed HEHE; 2) detailed medical records could be provided including records of each treatment, lab test and radiological images before and after each treatment; 3) patients should have regular follow-up including computed tomography (CT) or magnetic resonance imaging (MRI). Exclusion criteria: 1) EH of other sites instead of liver; 2) medical records or radiological images was not complete enough to analyze the outcome of the treatment. During the period, 58 HEHE patients were contacted. While 8 patients had incomplete medical records or radiological images which made the analysis on the outcome impossible, 50 patients were finally included. Informed consent has been obtained from each of them to use their clinical data for medical research.

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 test and radiological images. Patients' performance status was assessed according to Eastern Cooperative Oncology Group (ECOG). To analyze the outcome of observation, all patients with 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 ^[12]. For patients with curative-intent surgery or radiofrequency ablation (RF), radiological images (CT or MRI) during the follow-up period were evaluated to detect the recurrence. For patients with medicine treatment such as chemotherapy, targeted therapy, interferon- α 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 including observation and treatments, analysis of each management was carried out separately. The study was performed in accordance with the Declaration of Helsinki and approved by the Institutional Ethical Review Board of the China-Japan Friendship Hospital.

Statistical Considerations

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

For all the 50 HEHE patients, the median age at diagnosis was 36 years old (range: 21-61 years old) and the ratio of male was a little higher than female (54% vs 46%). Eighty percent of patients had no symptom and hepatic lesions were detected at routine examination. Ninety-six percent of patients had fully normal performance status (ECOG 0), while only 2 patients' performance status (ECOG 1) was mildly affected due to the existence of ascites. Seventy-six percent of patients were histologically diagnosed by percutaneous liver biopsy, while the others were histologically diagnosed by surgical resection or biopsy. The median length 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 of different managements.

Before histological diagnosis, all patient had contrast-enhanced radiology. Fifty-eight percent of patients had both contrast-enhanced CT and MRI, while the others had either contrast-enhanced CT or MRI. The results showed 94% patients had multiple

intrahepatic lesions and only 3 patients had single lesion. Extrahepatic metastases were detected in 54% patients and most of them were in the lung. Three patients had multiple sites metastases (one with lung + peritoneum metastases, one with lung + spleen metastases and one with lung + bone metastases). Radiological misdiagnosis was very common (82%) and 66% patients were misdiagnosed as hepatic metastatic carcinoma. Other misdiagnosis included intrahepatic cholangiocarcinoma, angiosarcoma and etc (Table 1). For most patients, serum liver functions were normal or mildly elevated. Abnormality of serum tumor marker was also rare among the group (Supplemental File 1).

Managements 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 routine examination. The median length of observation was 15.5 months (range 5-58 months). Sixteen (88.9%) of them had progressive disease (PD) and only 2 patients had stable disease (SD) with observation period of 22 months and 36 months, respectively. The brief profiles of 18 HEHE patients with initial observation were listed in Supplemental File 2.

Surgery, RF and TAE

Curative-intent surgery or RF was performed for 12 patients (6 male and 6 female; median age 42 with a range of 21-56 years old), including surgery for 7 patients and

RF for 5 patients (Table 2). Another 5 patients accepted surgery but only biopsy was performed. After surgery or RF, no adjuvant therapy was used for all the 12 patients. Ten patients (83.3%) had 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 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- α and Thalidomide

Six patients had the treatment of interferon- α (4 male and 2 female, age range 22-36 years old). The range of length with interferon- α treatment was 12-24 months and the results showed that 4 patients had partial response (PR), one patient had complete response (CR) and one patient had SD. Only mild adverse event was recorded for all the 6 patients (Table 3). Six patients had the treatment of thalidomide (4 male and 2 female, age range 32-61 years old). The range of length with thalidomide treatment was 12-48 months and the results showed that 4 patients had PD and 2 patients had SD. Moderate adverse event was recorded in 5 patients (4 patients with grade II paresthesia and one patient with grade II constipation), and both female patients had menolipsia after the treatment of thalidomide (Table 3). The brief profiles of radiological comparison for patients with treatment of interferon- α or thalidomide was listed in Supplemental File 3.

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 one had SD. One patient with PD chose targeted therapy after the failure of chemotherapy. The detailed chemotherapy regime was listed in Table 4. 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 one patient and bevacizumab + lenvatinib for one 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 4). Brief profiles of radiological comparison for patients with chemotherapy and targeted therapy were listed in Supplemental File 4.

Follow-up

All the 50 HEHE patients are alive and under close follow-up with radiological examination. The brief summary of outcomes of different managements was illustrated in Figure 2.

Discussion

HEHE is a very rare tumor intermediate between hemangioma and angiosarcoma in nature. Most patients discover their intrahepatic lesions 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 characteristics of HEHE ^[13-16], correct diagnosis solely based on radiology still seems difficult for both clinicians and radiologists because of the low incidence. In this study, 82% patients were misdiagnosed by contrast-enhanced CT and MRI.

For patients with HEHE, liver transplantation is an accepted therapeutic strategy with excellent outcomes ^[7, 17, 18]. However, due to the scarcity of donor, liver transplantation is only accessible for HEHE patients in critical condition. 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 ^[19]. In the majority of patients, curative resection is even implausible because of the multicentricity of the lesions or anatomic difficulties. Palliative resection is not advocated as a treatment method, because the tumor tend to behave aggressively after surgical resection ^[20, 21]. In this study, 7 patients accepted curative intent surgery and 5 of them had recurrence. Three patients recurred in a very short period. Meanwhile, patients who accepted curative intent RF showed the similar result. Four out of 5 patients recurred within 6 months after RF. The aggressive tumor behavior after resection or RF may be tumor cell reactivity to the hepatotrophic growth factors that promote hepatic regeneration, which makes both liver resection and RF cautious treatment options for HEHE patients.

Observation was suggested for HEHE patients, as the disease may keep stable or progress slowly ^[22]. In this study, 18 patients initially chose observation after

diagnosis and 88.9% of them had PD with a median length of 15.5 months.

Considering the indolent nature of the disease, observation could be an option for HEHE patients with relatively low tumor burden. But for HEHE patients with high tumor burden or fast progression, systematic treatment should be considered.

Currently, no standard systematic therapy is established for HEHE patients.

Chemotherapy, targeted therapy and immunotherapy have all been tried, however the results were variable ^[23-26]. Sorafenib has been reported to be effective to control the progression in several studies, but most of them are case reports ^[27, 28]. In one 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 ^[25]. No patients had sorafenib in this study. Three patients had treatment of apatinib and 2 of them had PR, which indicated the potential value of apatinib in the treatment of HEHE. Further clinical trial could be considered to verify this. Several cytotoxic chemotherapy regimens including adriamycin, dacarbazine, and paclitaxel have been reported effective for EH patients, but none of them were specific for HEHE patients ^[29-31]. In this study, 4 patients had diversified chemotherapy regime, while all of them had PD with moderate to severe adverse events. Due to the slow progression of HEHE and side effect of chemotherapy, cytotoxic chemotherapy regimens 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 ^[8, 32-35]. In this study, 6 patients had

the treatment of thalidomide and only 2 patients had SD. No tumor response (PR or CR) was achieved. The possible reason for this result could be the relatively low dosage of thalidomide. However, adverse events such as constipation, paresthesia and menolipsis made dosage increment intolerable for patients. Interferon- α therapy for EH has been also proposed for tumor reduction and metastasis prevention [9, 36, 37]. Kayler et al reported that interferon- α was used for treatment of metastatic HEHE after liver transplantation, observing palliation of symptoms and reduction of the lesions [38]. Interferon- α has been reported to have antiproliferative activity through cancer cell growth inhibition, activation of immune cells, inhibition of vascularization, and induction of cytokines [39, 40]. However, the clinical effect of interferon- α for HEHE patients has never been fully investigated. In this study, 6 patients with the treatment of interferon- α had an encouraging result including 4 PR, one CR and one SD. Only mild adverse events were recorded which showed the safety of interferon- α . Although the satisfying results of 6 patients with interferon- α can not guarantee the same effect on all HEHE patients, it does provide a promising option.

In conclusion, most HEHE patients were asymptomatic and misdiagnosed as hepatic metastatic carcinoma. During observation, most HEHE patients had progression. The risk of recurrence after curative intent surgery or RF was very high. In this study, interferon- α and apatinib were the treatments which induced tumor regression (PR or CR). The encouraging result of interferon- α makes it a promising option for HEHE patients and further clinical trial is needed.

Conflict of Interest Disclosures

The authors made no disclosures.

Data accessibility

All the detailed information of the study was described in Supplemental Files.

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Table 1 Radiological characteristics of HEHE patients

| Variables | HEHE 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 | |
| Single | 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%) |

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

Table 2 Information of HEHE patients with curative-intent 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 |

HEHE, hepatic epithelioid hemangioendothelioma

Table 3 Information of HEHE patients with treatment of interferon- α and thalidomide

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

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

Table 4 Information of HEHE 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 Apatinib | 4 cycles 22 months | PD PR | Emesis Grade III / Leukopenia Grade II Hand-Foot Syndrome Grade I / Diarrhea Grade I |
| 5 | Male | 30 | Apatinib | 5 months | PD | Hypertension Grade II Hand-Foot Syndrome Grade I / |
| 6 | Female | 38 | Apatinib | 14 months | PR | 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 Pembrolizumab + Bevacizumab + Lenvatinib | 8 cycles 8 cycles | PD | Leukopenia Grade I / Hypothyroidism |

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

Figure legends

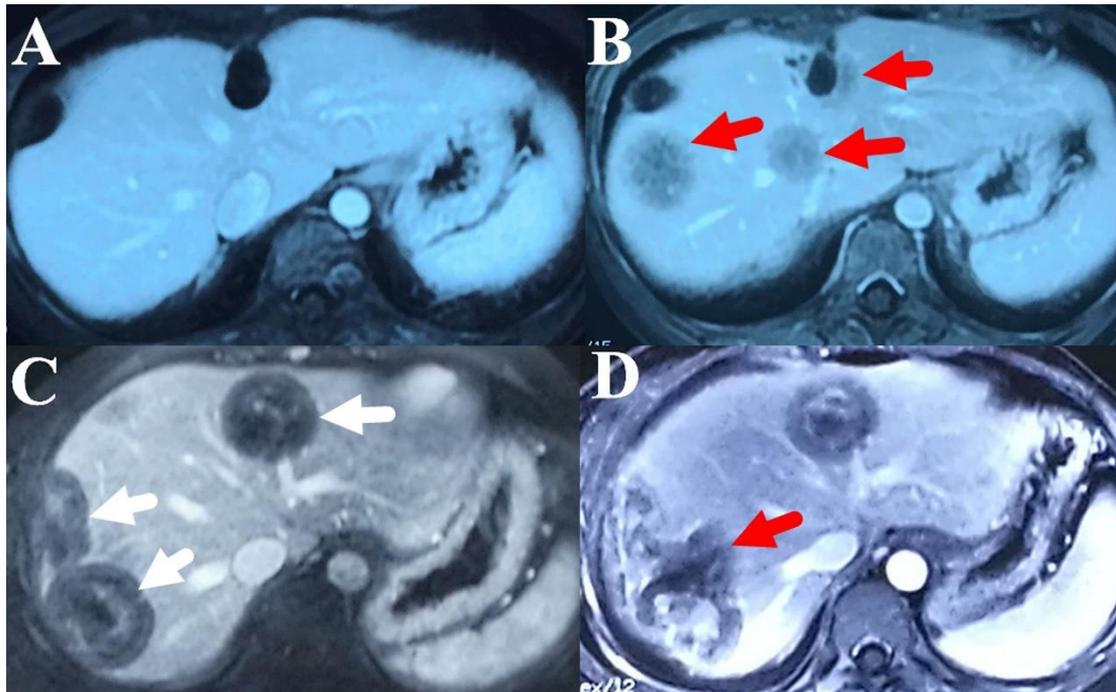


Figure 1: A and B: A 21 years old male HEH patient with surgical resection. **A:** No recurrence was detected at 6 months after surgery. **B:** Multi metastases were found at 20 months after surgery (marked by red arrows). **C and D:** A 32 years old HEH female with radiofrequency ablation (RF). **C:**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

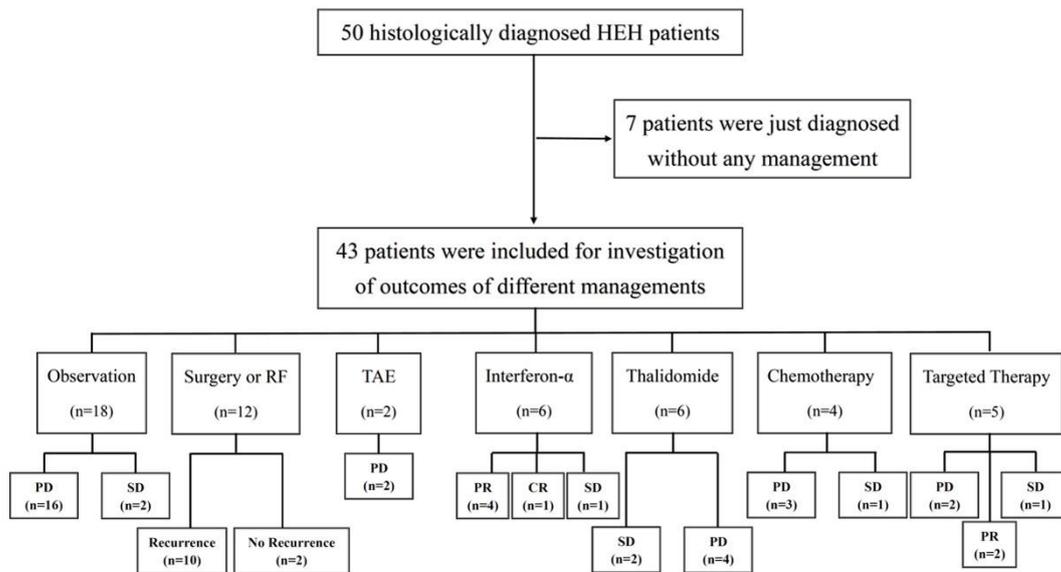


Figure 2: Brief summary of outcomes of HEH patients with different managements.

Figures

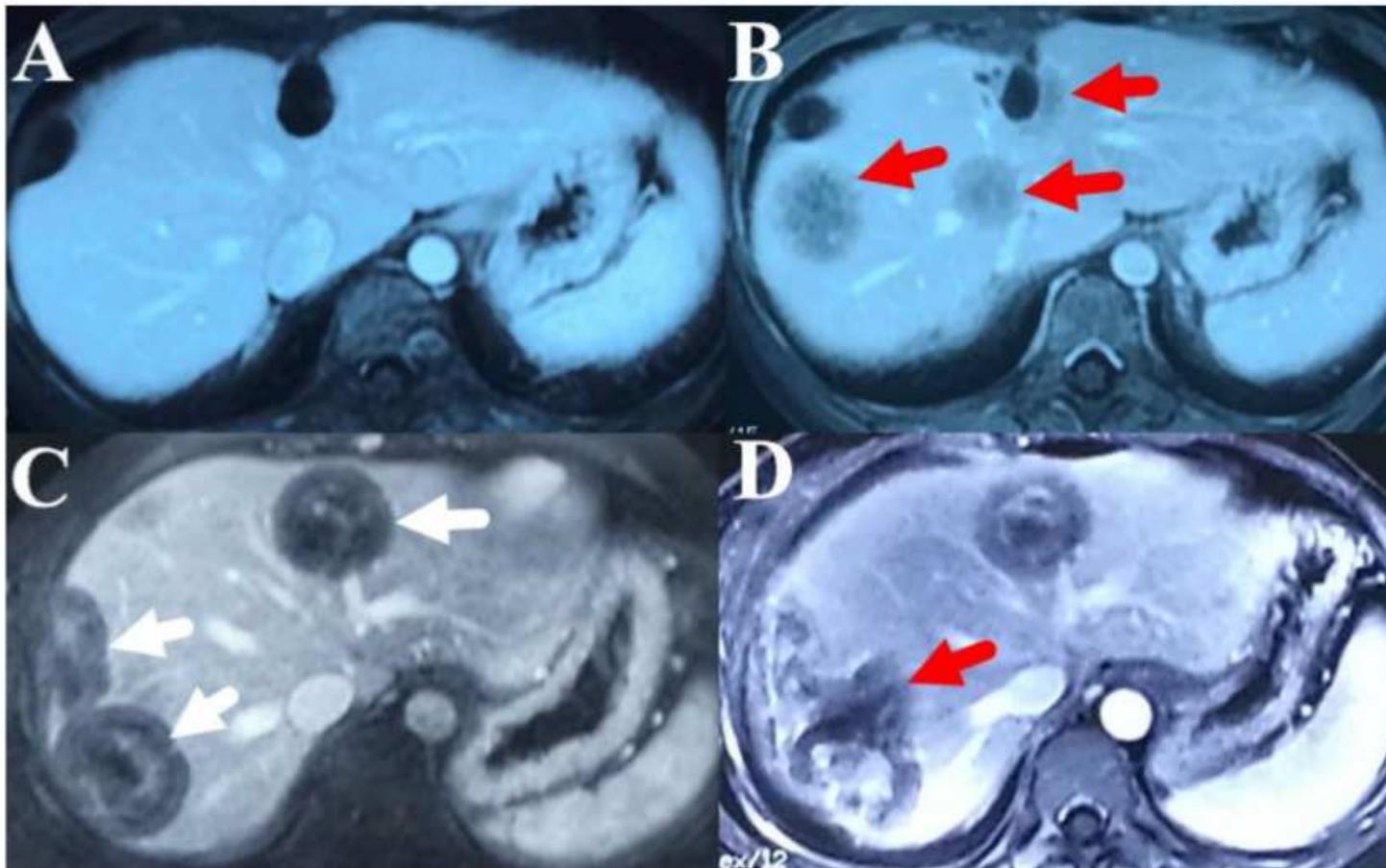


Figure 1

A and B: A 21 years 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 years 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).

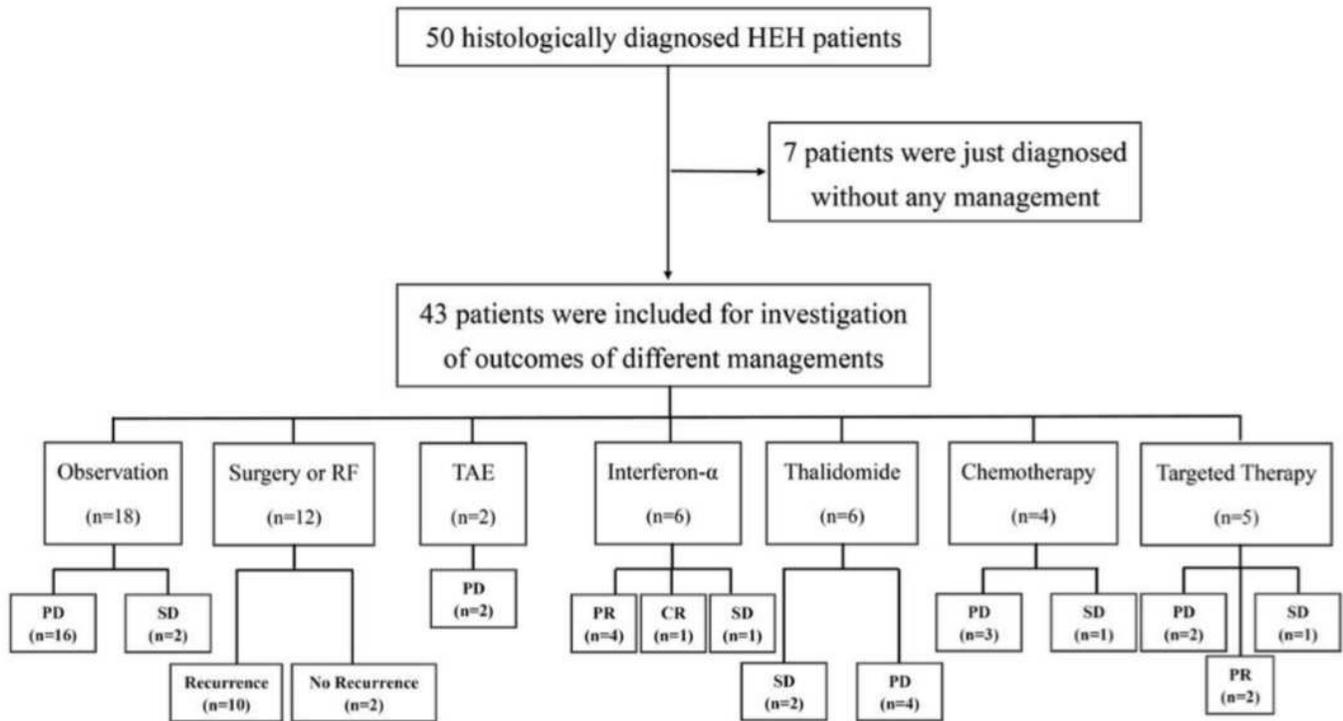


Figure 2

Brief summary of outcomes of HEH patients with different managements.

Supplementary Files

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