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Long-Term Outcomes Following Liver Transplantation for Hepatic Hemangioendothelioma: The UNOS Experience from 1987 to 2005

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Abstract
Introduction Hepatic hemangioendothelioma (HEH) is a vascular neoplasm with intermediate malignant potential. Outcomes after liver transplantation have only been reported as small, single-institution experiences. The purpose of this study was to evaluate patient and allograft survivals after liver transplantation in a large, multi-institutional cohort of patients with HEH.
Methods Using the United Network for Organ Sharing (UNOS) database, we identified 110 patients with a diagnosis of HEH who underwent 126 transplants between 1987 and 2005. Patient and allograft survivals were calculated using Kaplan–Meier survival curves. Log rank tests were used to determine the influence of study variables on outcomes.
Results Of the 110 transplanted patients, 75 patients (68%) were female, 80 patients (73%) were Caucasian, and the median age was 36 years old (23% < 4 y.o., 71% > 18 y.o.). The 30-day posttransplant mortality rate was 2.4%. At a median patient follow-up interval of 24 months, 1- and 5-year patient and allograft survivals were 80% and 64%, and 70% and 55%, respectively. Pretransplant medical status, but not age, was found to statistically correlate with patient survival.
Conclusion These data indicate that survivals after transplantation for HEH are favorable. Given the propensity for recurrence after resection, these data support consideration of liver transplantation for all patients with significant intrahepatic tumor burden.

Keywords Orthotopic liver transplantation · Hemangioendothelioma · Survival analysis

Introduction

Epithelioid hemangioendothelioma is a rare tumor of vascular origin that can involve soft tissues as well as visceral organs, including the liver, lung, spleen, stomach, and heart. Hepatic epithelioid hemangioendothelioma (HEH) is a common clinical form of the disease. The presentation of HEH, and the corresponding clinical course can vary widely. Some HEH tumors behave similar to benign hepatic hemangiomas, whereas others have a clinical course resembling highly aggressive angiosarcoma.

Some patients with hepatic HEH will present with limited intrahepatic disease; however, the majority have multifocal disease at diagnosis with extensive intrahepatic tumor burden and/or extrahepatic metastases. In a recent review of 434 HEH cases reported in the world literature, 87% of patients presented with bilobar and multifocal disease, and 37% of patients presented with extrahepatic involvement, including secondary disease of the lungs, regional lymph nodes, peritoneum, bone, spleen, and diaphragm.[1] Patients with extensive intrahepatic and extrahepatic tumor burden tend to have a more fulminate course, with rapid disease progression and secondary end-organ dysfunction.

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Patients with the less common presentation of limited intrahepatic disease are candidates for hepatectomy or other local treatments. For patients with limited intrahepatic disease, the overall recurrence rates observed after limited local treatments appear to be acceptable.[1] However, aggressive recurrence has been reported after minor hepatic resection of presumed localized disease,[2] as well as after major hepatic resection of multifocal disease.[3]

The frequent treatment failures observed after local therapy has prompted the use of orthotopic liver transplantation (OLT) in selected cases.[4–9] For patients with unresectable intrahepatic disease with or without extrahepatic disease, OLT combined with systemic therapy is the only treatment option. Single center studies reporting on outcomes after OLT in patients with extensive tumor burden, have documented favorable outcomes after transplantation with 5-year survivals ranging from 48% to 76%.[7–9] Even in patients with known extrahepatic disease, OLT can prolong survival by preventing death from liver failure.[1,10]

The best treatment strategy for patients with borderline resectable HEH has not been determined. To assess the utility of OLT in patients with extensive intrahepatic disease, this study evaluated patient and graft survivals after transplantation in a large, multi-institutional cohort of patients with HEH.

Material and Methods

Analysis of the United Network for Organ Sharing (UNOS)/Organ Procurement and Transplantation Network (OPTN) database identified 110 patients with a diagnosis of HEH who underwent a total of 126 transplants between 1987 and 2005. The majority of patients received their initial transplant during the more recent 10-year period from 1996 to 2005 (77 patients, 70%).

Examined study variables included recipient age, race, gender, ABO blood group, era of transplant, pretransplant medical status, patient and allograft survivals, and cause of allograft failure or death (cancer-related vs. other causes). Kaplan–Meier survival curves were used to calculate survivals and log-rank tests were used to determine the influence of study variables on survivals. A p value<0.05 was considered statistically significant.

Results

Demographic Data

Of the 110 patients transplanted for HEH, 75 patients (68%) were female. The most frequent race was Caucasian (73%), followed by Hispanic (13%), African American (8%), and Asian (6%) (Table 1). The median age at the time of first transplant was 36 years (range 0–70 years). There were 25 patients less than 4 years old and seven patients between the ages of 4 and 18 at the time of first transplant. During the study period, the number of OLTs performed per year in the US for HEH has increased, peaking at 16 in 2002. This progression is documented in Fig. 1.

Pretransplant Medical Condition

The median wait list time before the first transplant was 36 days (range 0–2,655 days). The blood group distribution of recipients was O: 47 patients, A: 40 patients, B: 17 patients, and AB: 6 patients. At the time of the first transplant 43 of the 110 patients (39%) were hospitalized and 21 of these 43 patients were in an intensive care unit. Twenty-five patients were listed as Status 1 at the time of transplant. Of the 110 study patients, 92 (84%) were transplanted before 2002 (i.e., before utilization of the Model for End Stage Liver Disease (MELD)/Pediatric End-stage Liver Disease (PELD) scoring system). For the 18

Table 1 Demographic and Clinical Summary of UNOS Database Patients Transplanted for Hepatic Epitheliod Hemangioendothelioma from 1987 to 2005

Study Variable	No. of Patients	Percent
Total	110	100
Sex		
Male	35	32
Female	75	68
Race		
Caucasian	80	73
Hispanic	14	13
Black	9	8
Asian	7	6
Medical requirements at first OLT		
ICU Care	22	20
Ventilator	11	10
Non-ICU hospitalization	21	19
Status 1 at First OLT	25	23
ABO blood group		
A1	39	36
A2	1	1
AB	6	5
B	17	15
O	47	43
Labs at first OLT		
SGPT (U/L)	34	7–1,859
Creatinine (mg/dL)	0.7	0.1–4.0
Bilirubin (mg/dL)	0.7	0.2–43.2
Albumin (G/dL)	3.7	1.5–4.8

Abbreviations: No, number; OLT, orthotopic liver transplant; ICU, intensive care unit, SGPT, Serum glutamic pyruvic transaminase

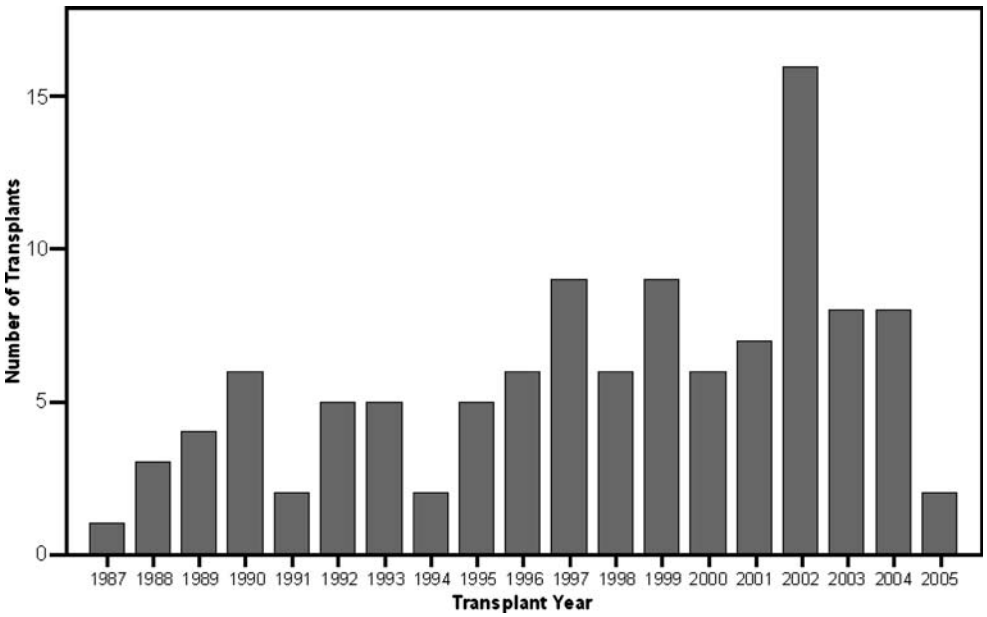

Figure 1 Progression of orthotopic liver transplantation for hepatic epithelioid hemangioendothelioma over time.

patients transplanted in the MELD/PELD era the median score was 27 (range 6–40). Biochemical parameters at the time of OLT for all study patients are recorded in Table 1.

Patient Survivals

The median length of posttransplant hospitalization was 16 days (range 0–156 days). There was one operative death, and two patients died within 30 days of transplant, yielding a 30-day mortality rate of 2.4%. At a median patient follow-up interval of 24 months (range 0–181 months), the 1-year, 3-year, and 5-year overall patient survivals were 80%, 68%, and 64%, respectively (Fig. 2). There were 31 actual 5-year survivors. Of the 38 patients who died during follow-up, 12 patients (32%) died of recurrent HEH, mainly involving distant sites.

Allograft Survivals

After first OLT, 12 patients (11%) required retransplantation, including four patients who received a third graft. Of the 17 operations for retransplantation, 10 (59%) were performed within 30 days of the previous operation. The indications for retransplant were available in 14 cases and included primary nonfunction (four transplants), vascular

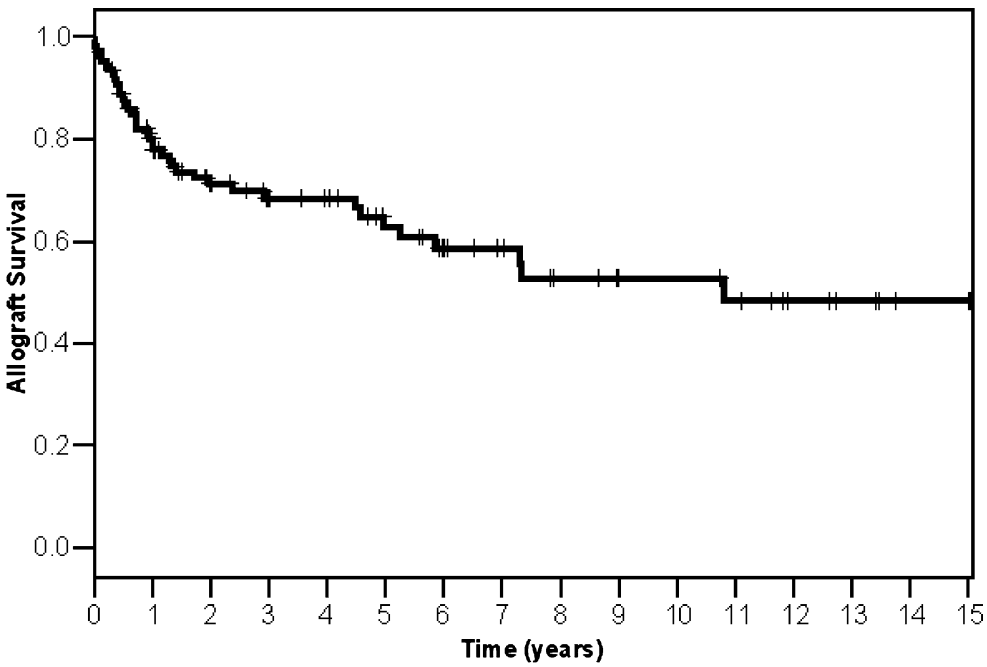

Figure 2 Kaplan–Meier plot of overall survivals for 110 patients treated with orthotopic liver transplantation for hepatic epitheliod hemangioma from 1987 to 2005.

thrombosis (three transplants), and biliary complications (two transplants). At a median allograft follow-up interval of 23 months (range 0–181 months), the 1-year, 3-year, and 5-year allograft survivals were 70%, 60%, and 55%, respectively (Fig. 3).

Patient Survivals Stratified by Age at First OLT

The patients presented in the UNOS/OPTN dataset had a bimodal age distribution. Of the 110 study patients, 25 patients (23%) were under age 4 (infantile HEH). Only seven patients (6%) were transplanted between the ages of 4 and 18 (pediatric HEH), and 78 patients (71%) were over age 18 (adult HEH). After OLT, patients with infantile HEH experienced 1-year, 3-year, and 5-year survivals of 68%, 61%, and 61%, respectively. Patients with adult HEH experienced similar outcomes with 1-year, 3-year, and 5-year survivals of 81%, 72%, and 67%, respectively (p=0.75) (Fig. 4, Table 2).

Analysis of Prognostic Factors

Univariate analysis was used to determine the impact of study variables on patient survivals. These comparisons determined that Status 1 designation, gender, age, and era of transplantation did not influence patient survivals. In contrast, other measures of pretransplant global medical condition, including the need for inpatient hospitalization and the need for intensive care unit management significantly impacted posttransplant survivals. Patients requiring hospitalization experience a 5-year posttransplant survival rate of only 44%, whereas outpatients experienced a 72% 5-year survival rate (p=0.01). Likewise, pretransplant intensive care unit patients had 5-year survivals of only 39%, compared to 65% for non-intensive care unit patients (p=0.02).

Discussion

Hepatic HEH is a rare tumor of vascular origin with variable malignant potential. No definitive etiologic factors have been confirmed, but possible causes include vinyl chloride, oral contraceptive use, asbestos, Thorotrast contrast, and alcoholic and viral hepatitis. Studies have consistently found that HEH occurs more frequently in women.[1,10] In one clinicopathologic study of 137 HEH cases, 61% of the patients were female and the mean age was 47 years.[10] The predominance of HEH in females, particularly during the reproductive years, suggests a hormonal association.[10]

Most patients present after the tumor burden becomes large enough to cause symptoms. In a recent series of 137 HEH patients, the diagnosis was made incidentally in only 22% of cases.[10] When symptomatic, the clinical presentation of HEH is nonspecific and includes right upper quadrant pain, hepatomegaly, and weight loss.[10] Tumor markers (AFP, CEA, CA 19-9) are usually in the normal range.[1] Computed tomography (CT) findings indicative of HEH include multiple hypo-attenuating tumors in both hepatic lobes that coalesce in a peripheral or subcapsular distribution with focal hepatic capsular retraction and, in larger lesions, a halo or target pattern of enhancement.[11,12]

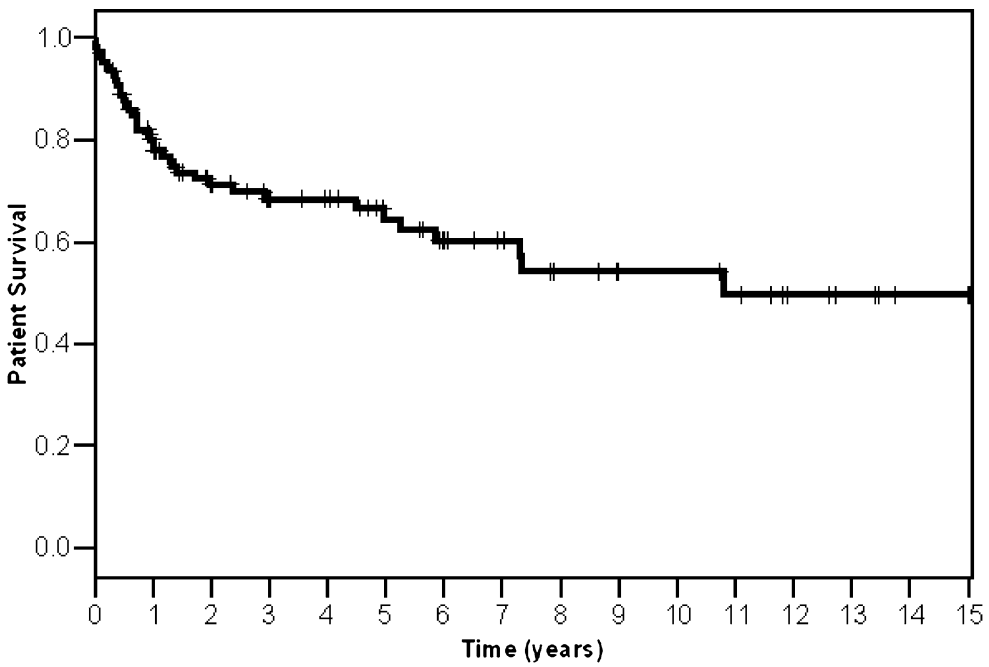

Figure 3 Kaplan–Meier plot of allograft survivals for 110 patients (126 transplants) treated with orthotopic liver transplantation for hepatic epitheliod hemangioma from 1987 to 2005.

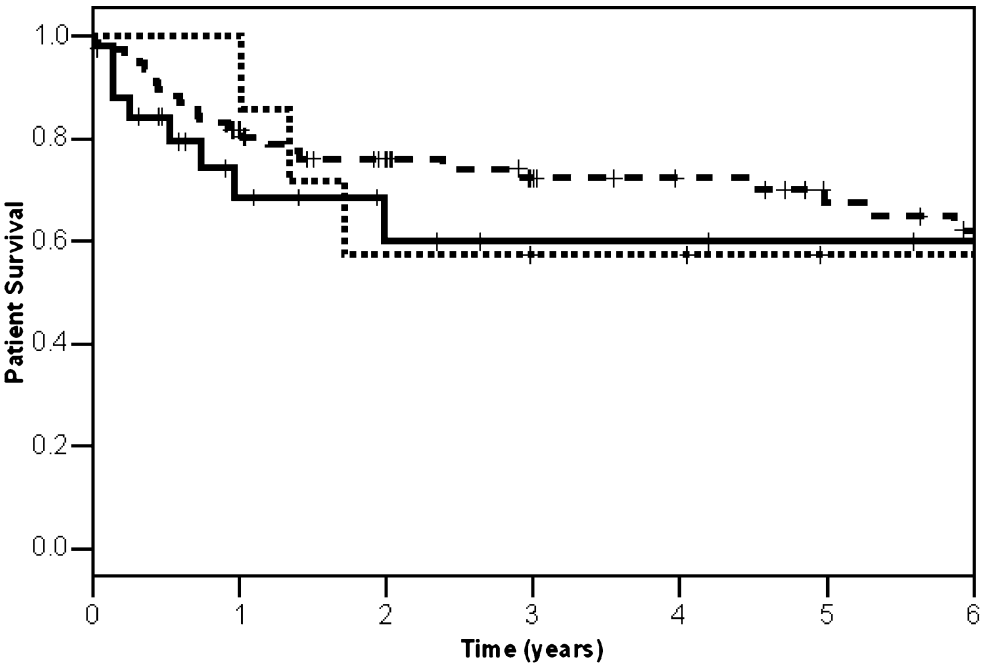

Figure 4 Patient survivals after orthotopic liver transplantation for hepatic epitheliod hemangioma stratified by age. Infantile (0–3 years old, *solid line*) vs. pediatric (4–18 years old, *dotted line*) vs. adult (>18 years old, *dashed line*).

A definitive diagnosis of HEH requires histopathologic assessment. Histologic characteristics include a well-developed basal lamina, the presence of Weibel–Palade bodies, and vascular invasion.[10,13] As histologic features of HEH may be similar to those of sclerosing hemangioma, angiosarcoma, cholangiocarcinoma, and metastatic carcinoma, the specificity of immunohistochemical examination is needed to supplement histologic examination.[10,13] Endothelial origin is confirmed by positive immuno-staining for factor VIII-related antigen and other endothelial cell markers.[13] Although helpful for diagnosis, no histopathologic features have been correlated with the disease's clinical behavior.

Currently, no prognostic clinical or histopathologic features have been identified that predict tumor aggressiveness. The only natural history data available for this disease comes from reports of untreated patients. In their review of the HEH world literature, Merhabi, et al.[1] determined that 25% of reported cases of HEH went untreated. More than half of these patients died of progressive disease and the 5-year survival for this cohort was only 5%. The unpredictable clinical course of HEH is further highlighted by specific reports of clinical outcomes after no treatment, including reports of extended survival with spontaneous tumor regression,[10,14] versus reports of rapid tumor progression leading to fulminant hepatic failure.[1,15]

For the rare patient who presents with limited intrahepatic disease, local treatment including liver resection is a logical treatment choice. Support for this approach comes from a recent review of all published series on HEH, which determined that the 5-year survival rate after resection for HEH was 75%.[1] However, because of the frequent multifocal nature of HEH at presentation, liver resection is rarely performed. In the above-mentioned review, only 19% of patients presented with unilobar disease, only 13% of patients presented with unifocal disease, and therefore, only 9.4% of these patients were candidates for liver resection.

Table 2 Posttransplant Survival Analysis for 110 Patients with Hepatic Hemangioendothelioma Stratified by Study Variables

Study Factor	*N*	Percent	Median Survival (months)	5-Year Survival (%)	*p* value
Sex					
Male	35	32	85.3	51	0.11
Female	75	68	>120	65	
Age					
Infantile (<4 years)	25	23	>120	61	0.75
Pediatric (4– 18 years)	7	6	>120	57	
Adult (19+ years)	78	71	>120	67	
Era					
1987–1995	33	30.0	>120	57	0.39
1996–2005	77	70.0	>120	57	
Preoperative medical condition					
Inpatient	43	39	63.7	44%	0.01
Outpatient	66	61	>120	72%	
ICU Care	22	20	22.8	39%	0.02
Non-ICU Care	87	80	>120	65%	
Status 1	25	23	>120	51%	0.36
Non-status 1	85	77	>120	63%	

Abbreviations: *N*, number of patients; ICU, intensive care unit

In the setting of more diffuse intrahepatic disease, major hepatic resection and OLT are the currently available treatment modalities.[2] Reports of tumor recurrence after liver resection are inconsistent. Whereas one case report has described success with major hepatic resection,[16] aggressive recurrence after resection of apparently localized lesions has also been reported.[2] It has been suggested that hepatotrophic, regenerative cellular signaling after hepatic resection may lead to rapid hyperproliferation of residual malignant disease in some patients.[2]

Instances of agressive disease recurrence and even fulminant hepatic failure have been reported following radical resection of multifocal HEH. In one recent study, radical resection of multifocal HEH was followed by multiple local recurrences, consumptive coagulopathy with thrombocytopenia, and death after resection.[3] Reports in the literature of "salvage" OLT, after noncurative resection, have also been disappointing.[2]

Based on the inability to predict the aggressiveness of HEH, the limited applicability of liver resection, and the reports of poor outcomes after resection of multifocal HEH, wider implementation of OLT should be considered. In the previously mentioned review of the world literature, 44.8% of patients were treated with OLT.[1] The 1-year and 5-year survivals in this cohort were 96% and 54%, respectively. Outcomes from the largest single-center cohort of patients transplanted for HEH were reported by Madariaga, et al. in 1995.[7] Five-year patient survival in this cohort of 16 patients was 71.3%. Five-year survival rates from other series in the literature include: Yokoyama et al.,[8] 48% (n=8) and Penn et al.,[17] 43% (n=21). In our analysis of the UNOS experience assessing 110 patients undergoing transplantation for HEH between 1987 and 2005, 1-year and 5-year allograft survivals were 70% and 55%, respectively, and 1-year and 5-year overall patient survivals were 80% and 64%, respectively.

Reported all-stage 5-year patient survival rates for HEH, regardless of therapy, are 41%,[1] 43%,[10] and 56%.[15] Given that the majority of patients who undergo OLT have advanced-stage disease with large tumor burden, achievement of 5-year patient survivals over 60% is remarkable. In addition, these outcomes compare favorably to those after OLT for other hepatic malignancies. Penn[17] reported that the HEH recurrence rate after OLT was only 33%, compared to 39% for non-incidental hepatoma, 44% for cholangiocarcinoma, 59% for metastatic tumors, and 64% for hemangiosarcoma. In our review of the UNOS database, 38 patients died during follow-up, with only 12 patients (11% of transplanted patients) having recurrent HEH as the primary cause of death.

The favorable outcomes after OLT in patients with HEH appear to be independent of patient age. Approximately 20% of the patients analyzed in this study were less than 4 years old. After OLT, this group with infantile HEH experienced survivals (5-year OS: 61%) similar to those of pediatric (5-year OS: 57%) and adult HEH patients (5-year OS: 67%). Although patient age did not have prognostic value, the analysis determined that the patient's medical condition before OLT was predictive of survival. Patients who were hospitalized, either in an ICU or non-ICU setting experienced significantly lower 5-year survival rates. These findings warrant consideration regarding patient selection for OLT listing and for donor-recipient matching.

Conclusions

This analysis indicates that liver transplantation for HEH is associated with favorable outcomes. Although liver resection and other local therapies may be reasonable choices in cases of small, focal lesions, the frequent presentation with multifocal disease often precludes the use of these treatments. Given the favorable outcomes after transplantation and the propensity for recurrence after liver resection, liver transplantation should be considered as a first-line treatment in patients who would otherwise require major hepatic resection, including selected patients with extrahepatic disease.

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